SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-122816- -00000-0000

Fecha: 2010-10-04 17:10:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 522

Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

10-122816

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: COMPUESTOS Y COMPOSICIONES COMO MODULADORES DE LA ACTIVIDAD DE TLR, UN MEDICAMENTO, MÉTODO PARA TRATAR UNA ENFERMEDAD, Y COMPOSICIONES INMINOGÉNICAS

SOLICITANTE: IRM LLC y NOVARTIS AG

DIRECCIÓN: 131 Front Street, P.O. Box HM 2899, Hamilton HM LX, Bermuda y Lichtstrasse 35, CH-4056 Basel

APODERADO: CARLOS R. OLARTE

BOGOTÁ 4 de Octubre de 2010

P2010/000122

03-10-2010

OLARTERAISBECK
OLARTE RAISBECK MOURE

Industria y Comercio
SUPERINTENDENCIA

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Act. 411-PRESENTACION Folios: 522

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2010/000122**

SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: IRM LLC y NOVARTIS AG
Dirección: 131 Front Street, P.O. Box HM 2899, Hamilton HM LX, Bermuda y Lichtstrasse 35, CH-4056 Basel
Nacionalidad o Domicilio: Bermuda y Suiza
Lugar de Constitución: Bermuda y Suiza
Teléfono: **Fax:**
E-mail:

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual
Número

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual
Número 79782747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2009/035563 Fecha Febrero 27, 2009

Publicación Internacional No. WO 2009/111337 Fecha Septiembre 11, 2009

(6) **Título (54)** **COMPUESTOS Y COMPOSICIONES COMO MODULADORES DE LA ACTIVIDAD DE TLR, UN MEDICAMENTO, MÉTODO PARA TRATAR UNA ENFERMEDAD, Y COMPOSICIONES INMUNOGÉNICAS** (folio 554)

Clasificación Internacional (51) C07D 221/12, C07D 471/04, C07D 471/12, C07D 491/056, C07D 491/12, C07D 495/04, A61K 31/4375, A61P 37/04

Prioridad **SI** [X] **NO** [ ]

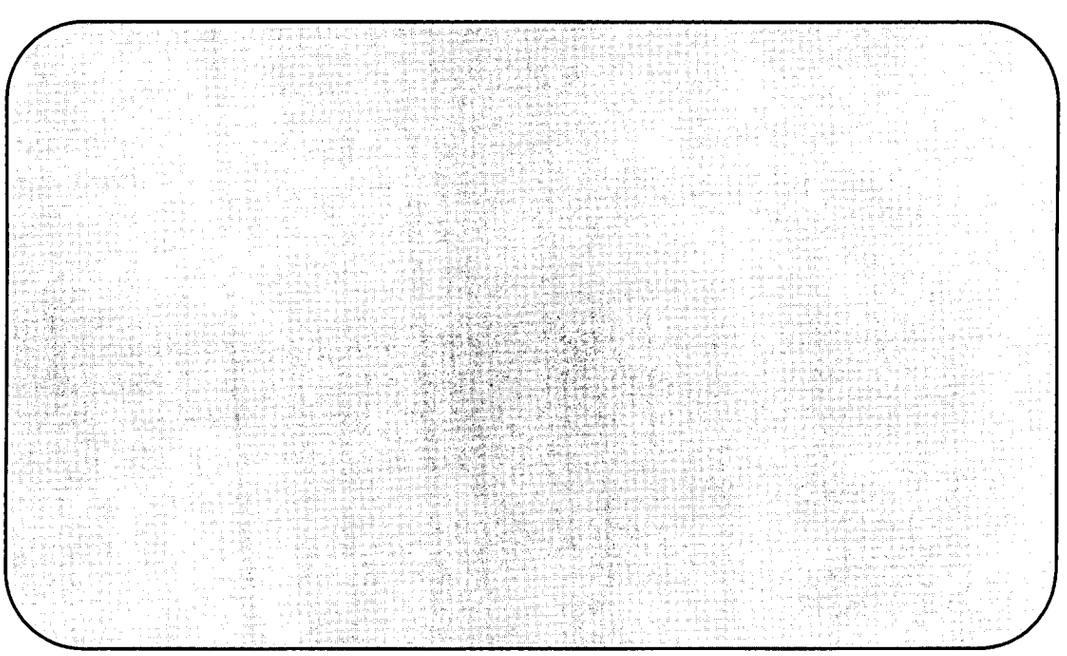
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Marzo 3, 2008	61/033.139
US	Enero 29, 2009	61/148.336

(9) **Comprobante de pago No.** 10- **Fecha** Octubre 4, 2010

ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 09-034.040
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] 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.
- [x] De ser el caso, modificaciones efectuadas a la solicitud internacional. PCT/IB306.
- [x] Otros. Búsqueda Internacional

(11) FIGURA CARACTERÍSTICA:



(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

LISTA DE INVENTORES

PCT/US2009/035563

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Nacionalidad: Estadounidense

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Estados Unidos
Nacionalidad: Estadounidense

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Act. 411 PRESENTACION Folios: 522

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 83,019
FECHA : OCTUBRE 4 DE 2010

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	353911714	04/10/2010	1,109,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	554,000.00
		TOTAL : $	554,000.00

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Traducción oficial de un documento que está originalmente en inglés

CERTIFICACIÓN

Yo, el suscrito Notario de Derecho Común de Basilea, Suiza, Dr. Matthias Staehelin, certifico por medio del presente que las firmas adjuntas previamente son las firmas genuinas de la señora Biljana Colovic, ciudadana de Serbia, residente en Basilea, Suiza; y del Doctor Georg von Sprecher, ciudadano de Luzein, Suiza, y Parpan, Suizak, residente en Oberwill/BL, Suiza, ambos actuando en nombre de IRM LLC, en Hamilton, Bermuda, ambos como titulares comisionados, ambos con firma conjunta.

La autenticidad de las firmas se estableció por comparación.

Basilea, Suiza, este día 14 (catorce) de diciembre de 2009 (dos mil nueve).

(Firmado) M. Staehelin, Notario

Sello: Dr. M. Staehelin, Notario

Protocolo de Legalización No. 3253/2009

Apostilla:

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

APOSTILLA:
(Convention de La Haye du 5 octobre 1961)

1. País:	Suiza

El presente documento público

2. Ha sido firmado por:	Doctor en Jurisprudencia. M. Staehelin
3. Actuando en calidad de:	Notario Público
4. Lleva el sello/estampilla de:	El anteriormente mencionado

Certificado

5. En:	Basilea.
6. El:	14 de diciembre de 2009
7. Por:	Cancillería municipal del Cantón de la ciudad de Basilea.
8. Bajo el No.:	8576/16899
9. Sello / estampilla:	Cancillería municipal · Ciudad de Basilea.
10. Firma:	Helena Schaffner

"FIN DE LA TRADUCCIÓN"

Certificación:
Certifico que la presente es una traducción auténtica y completa del inglés al español del documento adjunto, la cual he elaborado según mi leal saber y entender.
Documento: "IRM LLC – Certificación"
Fecha: 16 de enero de 2010.
Traductor: Jorge Enrique Sierra Reyes (Sello y firma digital debidamente registrados ante el Ministerio de Relaciones Exteriores de Colombia)
Licencia # 376 de 1993, expedida por el Ministerio de Justicia.
Dirección: Carrera 15 # 99-13 Of. 411, Bogotá, D.C.
Teléfonos: (571) 218 2308, (571) 623 2925.
E-mail: treseser1@yahoo.com
Traducción # 14-395

Traductor Oficial
JORGE E. SIERRA REYES
-encia 376 - 1993 Minjusticia

OLARTERAISBECK
OLARTE RAISBECK MOURE & CASTRO LTDA.

Carlos R. Ol
J. Ian Raisl
Juan Guillermo M
Natalia Ca
Alexander Agu
Catalina Barbastel
Ángela Co
Erika I
Carlos A. P
Andrés Alvai
Gina A
Juan Felipe Ac
Andrés Rin
Grace G
Mariana Fra
Of Co
Guillermo Ch
Graciela M
Jacqueline Chap
Cruz E. de Moncale

Power of Attorney

The undersigned,
IRM LLC
a Delaware Limited Liability Company

domiciled in
131 Front Street
Hamilton HM 12
Bermuda

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications, collect refunds, desist, settle, conciliate or negotiate. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

domiciliado en

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Juan Guillermo Moure y/o Natalia Castro** poder amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las **Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir, transigir, y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

IRM LLC

Signature/Firma:

Biljana Colovic Dr. Georg von Sprecher
Authorized Signatories

Date/Fecha: December 9, 2009
City,Country/Ciudad,País: Basel, Switzerland

8

Attestation

I, the undersigned Civil Law Notary in Basel, Switzerland, Dr. Matthias Staehelin, certify herewith that the signatures attached heretofore are the genuine signatures of **Ms. Biljana Colovic**, citizen of Serbia, residing in Basel, Switzerland, and **Dr. Georg von Sprecher**, citizen of Luzein, Switzerland, and Parpan, Switzerland, residing in Oberwil/BL, Switzerland, both acting for **IRM LLC**, in Hamilton, Bermuda, both as proxy holders, both with joint signature.

The authenticity of the signatures was established by means of comparison.

BASEL, Switzerland, this 14th (fourteenth) day of December 2009 (two thousand and nine)

M. Staehelin, Notar

Dr. M. Staehelin
Notar

Leg.Prot.Nr. 3253 /2009

APOSTILLE
(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz/Suisse)
This official document
2. is signed by ..... Dr. iur. M. Staehelin
3. in his/her function as ... notary public
and certified by the seal of the ..... above mentioned

STATE CHANCERY * BASLE-CITY *

5. in Basel (Bâle) 6. on Certified 14. Dez. 2009
7. by the State Chancery of the Canton of Basel-Stadt .....
8. no. 8576/16899
9. Seal/stamp:
10. Signature: .....
Helena Schaffner

TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS

Nota del traductor:

El documento adjunto de poder de Novartis AG a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro lleva los siguientes datos en inglés.

CERTIFICACIÓN NOTARIAL

1. En esta fecha, día 30 de Agosto de 2006, yo, el suscrito Notario Público certifico por medio del presente la autenticidad de las firmas del señor Arthur Canonica, ciudadano de Corticiasca, Suiza, residente en Wisen/SO, Suiza, y del Sr. Pascal Traub, ciudadano de Riehen, Suiza, residente en Basilea, Suiza, ambos personas mayores de edad y con dirección comercial en Lichstrasse 35, 4056, Basilea, Suiza. La autenticidad de la firmas fue establecida por medio de la comparación.
2. Además, yo, el Notario Público, certifico por el presente que las anteriores personas han ejecutado el anterior documento como apoderados de Novartis AG.
3. Además, yo, el Notario Público certifico por el presente que Novartis AG, con su principal lugar de negocios en Basilea, Suiza, está debidamente constituida, está actualmente vigente y que los propósitos para los cuales se otorgó el Documento de Poder están dentro del alcance de sus propósitos corporativos.

Traductor O.
JORGE E. SIERR
Licencia 376 - 1992

4. Además, yo, el Notario Público, certifico por el presente que las anteriores personas tienen la autoridad para ejecutar el documento de Poder y que por este instrumento, su representación es legal.

La base para mis certificaciones de los puntos 2, 3 y 4 fue la exhibición de los siguientes documentos auténticos:

- Documento de Poder de Novartis AG fechado el 19 de junio de 2006 y
- Extracto del Registro de Comercio del Cantón de la ciudad de Basilea para Novartis AG, en Basilea, fechado el 25 de enero de 2006.

Basilea, Suiza, este día 30 de Agosto de 2006.

(Firmado) Dr. Matthias Staehelin, Notario Público del Cantón de la ciudad de Basilea, Suiza.

Mi licencia vence el 11 de Marzo de 2009.

Hay una Apostilla de Suiza, firmada por Heidi Fischer, bajo el No. 8049/13584.

Traductor Ofic
JORGE E. SIERRA
Licencia 376 - 1993

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Novartis"

Fecha: 12 de Septiembre de 2006.

Traductor: Jorge Enrique Sierra Reyes.

Licencia No. 376 de 1993, del Ministerio de Justicia.

Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.

Teléfono: (57-1) 2182308, (57-1) 6232925.

E-mail: treseser1@yahoo.com. No. 8346

Traductor Of.
JORGE E. SIERRA
Licencia 376 - 1993

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olar
J. Ian Raisbe
Ana María Fri
Juan Guillermo Mou
Natalia Cast

Zayde Chah
Jacqueline Chapar
José Luis Londoi
Felipe Mendo
Simón Salio

Of Coun
Guillermo Chah
Graciela Me

Power of Attorney

The undersigned,

domiciled in

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

NOVARTIS AG

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las **Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma: Arthur Canonica Pascal Traub

Date/Fecha: June 27, 2006

City,Country/Ciudad,País: Basel, Switzerland

World Trade Center - Torre A, Calle 100 No. 8A – 37, Piso 10, Bogotá D.C., Colombia
Tel + 57 1 601-7700, Fax + 57 1 601-7799, office@olarteraisbeck.com, www.olarteraisbeck.com

Attestation

1 On this date, the 30th (thirtieth) day of August 2006 (two thousand and six), I, the undersigned Notary Public certify herewith the authenticity of the signatures of **Mr. Arthur Canonica**, citizen of Corticiasca, Switzerland, residing in Wisen/SO, Switzerland and of **Mr. Pascal Traub**, citizen of Riehen, Switzerland, residing in Basel, Switzerland, both of legal age and with business address at, Lichtstrasse 35, 4056 Basel, Switzerland. The authenticity of the signatures was established by means of comparison.

2 Further, I, the Notary Public certify herewith that the foregoing persons have executed the foregoing document as proxy holders for Novartis AG.

3 Further, I, the Notary Public certify herewith that Novartis AG, having its principal place of business located in Basel / Switzerland, is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4 Further, I, the Notary Public certify herewith that the foregoing persons have the authority to execute the Power of Attorney and that for this instrument their representation is legal.

The foundation for my certifications contained in points 2 (two), 3 (three) and 4 (four) was the exhibition of the following authentic documents:

- Power of Attorney by Novartis AG dated June 19 (nineteen), 2006 (two thousand and six); and
- Extract from the Register of Commerce of the Canton of Basel-City for Novartis AG, in Basel, dated January 25 (twenty-five), 2006 (two thousand and six).

BASEL, Switzerland, this 30th (thirtieth) day of August 2006 (two thousand and six)

Dr. Matthias Staehelin, Notary Public
in the Canton of Basel-City, Switzerland

My license expires on March 11 (eleven), 2009 (two thousand and nine).

Reg.Prot.Nr. 975 /2006

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 September 2009 (11.09.2009)

PCT

(10) International Publication Number
WO 2009/111337 A1

(51) International Patent Classification:
C07D 221/12 (2006.01) *C07D 491/12* (2006.01)
C07D 471/04 (2006.01) *C07D 495/04* (2006.01)
C07D 471/12 (2006.01) *A61K 31/4375* (2006.01)
C07D 491/056 (2006.01) *A61P 37/04* (2006.01)

(21) International Application Number:
PCT/US2009/035563

(22) International Filing Date:
27 February 2009 (27.02.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/033,139 3 March 2008 (03.03.2008) US
61/148,336 29 January 2009 (29.01.2009) US

(71) Applicants *(for all designated States except US)*: **IRM LLC** [US/US]; 131 Front Street, P.O. Box 2899, HM LX Hamilton (BM). **NOVARTIS AG.** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventors; and
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR,

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(54) Title: COMPOUNDS AND COMPOSITIONS AS TLR ACTIVITY MODULATORS

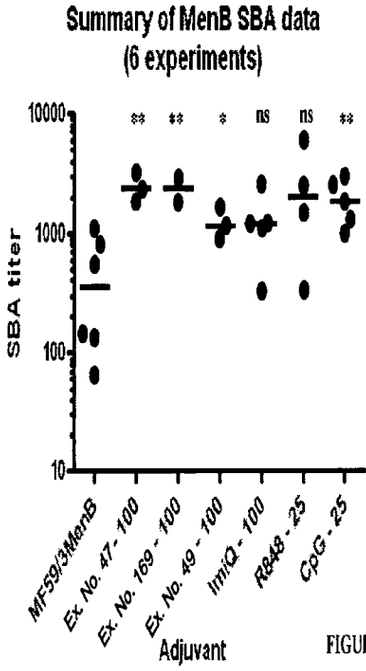
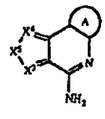


FIGURE 5



(I)

(57) Abstract: The invention provides a novel class of compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with Toll-Like Receptors, including TLR7 and TLR8. In one aspect, the compounds are useful as adjuvants for enhancing the effectiveness of a vaccine (formula I) wherein: X^3 is N; X^4 is N Or CR^3; X^5 is $-CR^4=CR^5$.

WO 2009/111337 A1

KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, 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, ST, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, 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 (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

COMPOUNDS AND COMPOSITIONS AS TLR ACTIVITY MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority under 35 U.S.C. §119(e) to U.S. Provisional Patent Application No. 61/033,139, filed March 3, 2008 and U.S. Provisional Patent Application No. 61/148,336, filed January 29, 2009. The disclosure of the priority applications are incorporated herein by reference in their entirety and for all purposes.

STATEMENT OF GOVERNMENT SUPPORT

[0002] This invention was made in part with Government support under DTRA Grant No. HDTRA1-07-9-0001 awarded by the Department of Defense. The Government has certain rights in the invention.

FIELD OF THE INVENTION

[0003] The invention relates to modulators of Toll-Like Receptors (TLRs), and methods of using such compounds.

BACKGROUND OF THE INVENTION

[0004] Early detection of specific classes of pathogens is accomplished by the innate immune system with the help of pattern recognition receptors (PRRs). The detected pathogens include viruses, bacteria, protozoa and fungi, and each constitutively expresses a set of class-specific, mutation-resistant molecules called pathogen-associated molecular patterns (PAMPs). These molecular markers may be composed of proteins, carbohydrates, lipids, nucleic acids or combinations thereof, and may be located internally or externally. Examples of PAMPs include bacterial carbohydrates (lipopolysaccharide or LPS, mannose), nucleic acids (bacterial or viral DNA or RNA), peptidoglycans and lipotechoic acids (from Gram positive bacteria), *N*-formylmethionine, lipoproteins and fungal glucans.

[0005] Pattern recognition receptors have evolved to take advantage of three PAMP qualities. First, constitutive expression allows the host to detect the pathogen regardless of its life cycle stage. Second, the PAMPs are class specific, which allows the host to distinguish between pathogens and thereby tailor its response. Third, mutation resistance allows the host to recognize the pathogen regardless of its particular strain.

[0006] Pattern recognition receptors are involved in more than just recognition of pathogens via their PAMPs. Once bound, pattern recognition receptors tend to cluster, recruit other extracellular and intracellular proteins to the complex, and initiate signaling cascades that

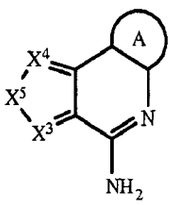
ultimately impact transcription. Additionally, pattern recognition receptors are involved in activation of complement, coagulation, phagocytosis, inflammation, and apoptosis functions in response to pathogen detection.

[0007] Pattern recognition receptors (PRRs) may be divided into endocytic PRRs or signaling PRRs. The signaling PRRs include the large families of membrane-bound Toll-like receptors (TLRs) and cytoplasmic NOD-like receptors, while the endocytic PRRs promote the attachment, engulfment and destruction of microorganisms by phagocytes without relaying an intracellular signal, are found on all phagocytes and mediate removal of apoptotic cells. In addition, endocytic PRRs recognize carbohydrates and include mannose receptors of macrophages, glucan receptors present on all phagocytes and scavenger receptors that recognize charged ligands.

SUMMARY OF THE INVENTION

[0008] Provided herein are compounds and pharmaceutical compositions thereof, which are useful modulators of toll-like receptors.

[0009] In one aspect provided herein such compounds, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, having a structure according to Formula (I) as described herein. Certain embodiments of the invention include compounds of Formula (I-A), methods of using them, and pharmaceutical compositions comprising these compounds:



Formula (I-A)

wherein:

X^3 is N; X^4 is N or CR^3, and X^5 is $-CR^4=CR^5-$;

R^1 and R^2 are H; R^3 is H;

R^4 and R^5 are each independently selected from H, halogen, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-SR^7$, $-(CH_2)_nOR^7$, $-(CH_2)_nR^7$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, $-C_1$-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-

C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, -NO_2, -R^7, -OR^8, -$C(O)R^8$, -$OC(O)R^8$, -$C(O)OR^8$, -$N(R^9)_2$, -$P(O)(OR^8)_2$, -$OP(O)(OR^8)_2$, -$P(O)(OR^{10})_2$, -$OP(O)(OR^{10})_2$, -$C(O)N(R^9)_2$, –$S(O)_2R^8$, –$S(O)_2N(R^9)_2$, and -$NR^9S(O)_2R^8$; or R^3 and R^4, or R^4 and R^5, when present on adjacent ring atoms, can optionally be linked together to form a 5-6 membered ring, wherein the 5-6 membered ring is optionally substituted with R^7;

each L is independently selected from a bond, -$(O(CH_2)_m)_t$-, C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene, wherein the C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene of L are each optionally substituted with 1 to 4 substituents independently selected from halogen, -R^8, -OR^8, -$N(R^9)_2$, -$P(O)(OR^8)_2$, -$OP(O)(OR^8)_2$, -$P(O)(OR^{10})_2$, and -$OP(O)(OR^{10})_2$;

R^7 is selected from H, C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, and C_3-C_8heterocycloalkyl groups of R^7 are each optionally substituted with 1 to 3 R^{13} groups, and each R^{13} is independently selected from halogen, –CN, -LR^9, -LOR^9, -OLR^9, -LR^{10}, -LOR^{10}, -OLR^{10}, -LR^8, -LOR^8, -OLR^8, -LSR^8, -LSR^{10}, -$LC(O)R^8$, -$OLC(O)R^8$, -$LC(O)OR^8$, -$LC(O)R^{10}$, -$LOC(O)OR^8$, -$LC(O)NR^9R^{11}$, -$LC(O)NR^9R^8$, -$LN(R^9)_2$, -LNR^9R^8, -LNR^9R^{10}, -$LC(O)N(R^9)_2$, –$LS(O)_2R^8$, -$LS(O)R^8$, -$LC(O)NR^8OH$, -$LNR^9C(O)R^8$, -$LNR^9C(O)OR^8$, –$LS(O)_2N(R^9)_2$, -$OLS(O)_2N(R^9)_2$, -$LNR^9S(O)_2R^8$, -$LC(O)NR^9LN(R^9)_2$, -$LP(O)(OR^8)_2$, -$LOP(O)(OR^8)_2$, -$LP(O)(OR^{10})_2$ and -$OLP(O)(OR^{10})$;

each R^8 is independently selected from H, -$CH(R^{10})_2$, C_1-C_8alkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, C_1-C_6hydroxyalkyl and C_1-C_6haloalkoxy, wherein the C_1-C_8alkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, C_1-C_6hydroxyalkyl and C_1-C_6haloalkoxy groups of R^8 are each optionally substituted with 1 to 3 substituents independently selected from –CN, R^{11}, -OR^{11}, -SR^{11}, -$C(O)R^{11}$, -$OC(O)R^{11}$, -$C(O)N(R^9)_2$, -$C(O)OR^{11}$, -$NR^9C(O)R^{11}$, -NR^9R^{10}, -$NR^{11}R^{12}$, -$N(R^9)_2$, -OR^9, -OR^{10}, -$C(O)NR^{11}R^{12}$, -$C(O)NR^{11}OH$, –$S(O)_2R^{11}$, –$S(O)R^{11}$, –$S(O)_2NR^{11}R^{12}$, -$NR^{11}S(O)_2R^{11}$, -$P(O)(OR^{11})_2$, and -$OP(O)(OR^{11})_2$;

each R^9 is independently selected from H, -$C(O)R^8$, -$C(O)OR^8$, -$C(O)R^{10}$, -$C(O)OR^{10}$, -$S(O)_2R^{10}$, -C_1-C_6 alkyl, C_1-C_6 heteroalkyl and C_3-C_6 cycloalkyl, or each R^9 is independently a C_1-C_6alkyl that together with N they are attached to form a C_3-C_8heterocycloalkyl, wherein the C_3-

C_8heterocycloalkyl ring optionally contains an additional heteroatom selected from N, O and S, and wherein the C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, or C_3-C_8heterocycloalkyl groups of R^9 are each optionally substituted with 1 to 3 substituents independently selected from –CN, R^{11}, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-OC(O)R^{11}$, $-C(O)OR^{11}$, $-NR^{11}R^{12}$, $-C(O)NR^{11}R^{12}$, $-C(O)NR^{11}OH$, $-S(O)_2R^{11}$, $-S(O)R^{11}$, $-S(O)_2NR^{11}R^{12}$, $-NR^{11}S(O)_2R^{11}$, $-P(O)(OR^{11})_2$, and $-OP(O)(OR^{11})_2$;

each R^{10} is independently selected from aryl, C_3-C_8cycloalkyl, C_3-C_8heterocycloalkyl or a heteroaryl, wherein the aryl, C_3-C_8cycloalkyl, C_3-C_8heterocycloalkyl or heteroaryl groups are optionally substituted with 1 to 3 substituents selected from halogen, $-R^8$, $-OR^8$, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9CO_2R^8$, $-CO_2R^8$, $-C(O)R^8$ and $-C(O)N(R^9)_2$;

R^{11} and R^{12} are independently selected from H, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl groups of R^{11} and R^{12} are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, R^8, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-NR^8C(O)R^8$, $-NR^8C(O)OR^8$, $-C(O)N(R^9)_2$, C_3-C_8heterocycloalkyl, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, $-NR^9S(O)_2R^8$, C_1-C_6haloalkyl and C_1-C_6haloalkoxy, and wherein the aryl and heteroaryl groups of R^{11} and R^{12} are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, R^8, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-C(O)N(R^9)_2$, C_3-C_8heterocycloalkyl, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, $-NR^9S(O)_2R^8$, C_1-C_6haloalkyl and C_1-C_6haloalkoxy; or R^{11} and R^{12} are each independently C_1-C_6alkyl and taken together with the N atom to which they are attached form an optionally substituted C_3-C_8heterocycloalkyl ring optionally containing an additional heteroatom selected from N, O and S;

Ring A is an aryl or a heteroaryl, wherein the aryl and heteroaryl groups of Ring A are optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH{=}CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$; or two adjacent R^A substituents on Ring A form a 5-6 membered ring that contains up to two heteroatoms as ring members; n is, independently at each occurrence, 0, 1, 2, 3, 4, 5, 6, 7 or 8; each m is independently selected from 1, 2, 3, 4, 5 and 6, andt is 1, 2, 3, 4, 5, 6, 7 or 8.

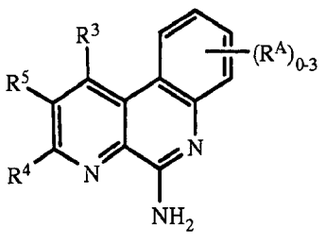
[00010] In certain embodiments of such compounds of Formulas (I) or (I-A), one of R^4 and R^5 is H; and the other of R^4 and R^5 is selected from halogen, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, $-SR^7$, $-(CH_2)_nOR^7$, $-(CH_2)_nR^7$, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, $-R^7$, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-C(O)N(R^9)_2$, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, and $-NR^9S(O)_2R^8$.

[00011] In certain embodiments of such compounds of Formulas (I) or (I-A), Ring A is phenyl, naphthyl, fluorenyl, indenyl, azulenyl or anthracenyl, each of which is optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$. In certain embodiments of such compounds of Formulas (I) or (I-A), Ring A is phenyl or naphthyl.

[00012] In certain embodiments of the such compounds of Formulas (I) or (I-A), Ring A is benzofuranyl, benzofurazanyl, benzoxazolyl, benzopyranyl, benzthiazolyl, benzothienyl, benzazepinyl, benzimidazolyl, benzothiopyranyl, benzo[1,3]dioxole, benzo[b]furyl, benzo[b]thienyl, cinnolinyl, furazanyl, furyl, furopyridinyl, imidazolyl, indolyl, indolizinyl, indolin-2-one, indazolyl, isoindolyl, isoquinolinyl, isoxazolyl, isothiazolyl, 1,8-naphthyridinyl, oxazolyl, oxaindolyl, oxadiazolyl, pyrazolyl, pyrrolyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinoxalinyl, quinolinyl, quinazolinyl, 4H-quinolizinyl, thiazolyl, thiadiazolyl, thienyl, triazinyl,triazolyl or tetrazolyl, each of which is optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-$

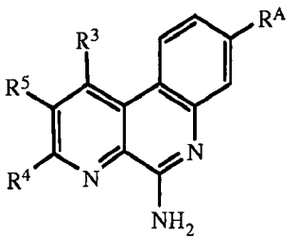
$C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$. In certain embodiments of such compounds of Formulas (I) or (I-A), Ring A is pyridyl, benzo[1,3]dioxole, thienyl, benzothienyl, benzofuranyl, or indolyl.

[00013] In certain embodiments of compounds of Formulas (I) and Formula (I-A), the compounds have a structure of Formula (X-A):



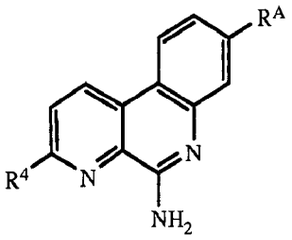
Formula (X-A).

[00014] In certain embodiments of compounds of Formulas (I) or Formula (I-A), the compounds have a structure of Formula (XI):

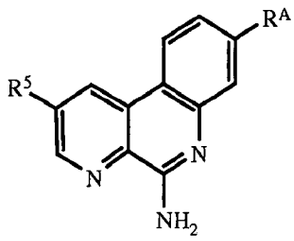


Formula (XI).

[00015] In certain embodiments of compounds of Formulas (I) or Formula (I-A), the compound have a structure of Formula (XII) or Formula (XIII):



Formula (XII)

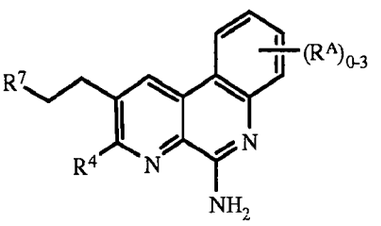


Formula (XIII).

[00016] In certain embodiments of such compounds of Formulas (I) or (I-A), Formulas (X-A) and (XI) to (XIII), R^4 and R^5 are independently selected from H, halogen, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, $-SR^7$, $-(CH_2)_nR^7$, $-(CH_2)_nOR^7$, $-C_1$-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy, wherein the

C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, -R^7, -OR^8, -$C(O)R^8$, -$OC(O)R^8$, -$C(O)OR^8$, -$N(R^9)_2$, -$P(O)(OR^8)_2$, -$OP(O)(OR^8)_2$, -$P(O)(OR^{10})_2$, -$OP(O)(OR^{10})_2$, -$C(O)N(R^9)_2$, –$S(O)_2R^8$, –$S(O)_2N(R^9)_2$, and -$NHS(O)_2R^8$. In other embodiments of such compounds of Formulas (I) or (I-A), Formulas (X-A) and (XI) to (XIII), R^4 and R^5 are independently selected from H, halogen, -$C(O)OR^7$, -$C(O)R^7$, -$C(O)N(R^{11}R^{12})$, -$N(R^{11}R^{12})$, -$N(R^9)_2$, -$NHN(R^9)_2$, -LR^8, -LR^{10}, -OLR^8, -OLR^{10}, -SR^7, -$(CH_2)_nOR^7$, -$(CH_2)_nR^7$, -C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy, wherein the -C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy groups are each optionally substituted with R^7.

[00017] In certain embodiments of compounds of Formulas (I) and Formula (I-A), the compounds have a structure of Formula (XIV):



Formula (XIV).

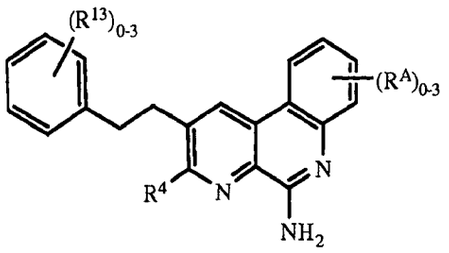
[00018] In certain embodiments of such compounds of Formulas (XIV) R^4 is selected from H, halogen, -$C(O)OR^7$, -$C(O)R^7$, -$C(O)N(R^{11}R^{12})$, -$N(R^{11}R^{12})$, -SR^7, -$(CH_2)_nR^7$, -$(CH_2)_nOR^7$, -C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy, wherein the C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, -R^7, -OR^8, -$C(O)R^8$, -$OC(O)R^8$, -$C(O)OR^8$, -$N(R^9)_2$, -$P(O)(OR^8)_2$, -$OP(O)(OR^8)_2$, -$P(O)(OR^{10})_2$, -$OP(O)(OR^{10})_2$, -$C(O)N(R^9)_2$, –$S(O)_2R^8$, –$S(O)_2N(R^9)_2$, and -$NHS(O)_2R^8$. In other embodiments of such compounds of Formulas (XIV), R^4 is selected from H, halogen, -$C(O)OR^7$, -$C(O)R^7$, -$C(O)N(R^{11}R^{12})$, -$N(R^{11}R^{12})$, -SR^7, -$(CH_2)_nOR^7$, -$(CH_2)_nR^7$, -C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy, wherein the -C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy groups are each optionally substituted with R^7.

[00019] In certain embodiments of such compounds of Formulas (I) or (I-A), Formulas (X-A) and (XI) to (XIV), R^7 is selected from H, C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl and C_3-C_8heterocycloalkyl groups of R^7 are each optionally substituted with 1 to 3 R^{13} groups and each R^{13} is independently selected from halogen, –CN, -LR^9, -LOR^9, -OLR^9, -LR^{10}, -LOR^{10}, -OLR^{10}, -LR^8,

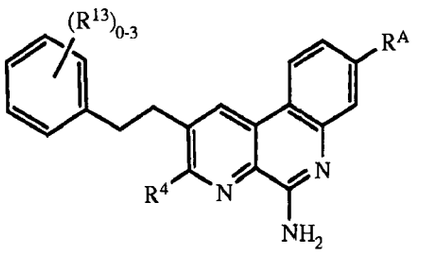
-LOR^8, -OLR^8, -LSR^8, -LSR^{10}, -LC(O)R^8, -OLC(O)R^8, -LC(O)OR^8, -LC(O)R^{10}, -LOC(O)OR^8, -LC(O)NR^{9}R^{11}, -LC(O)NR^{9}R^8, -LN(R^9)$_2$, -LNR^{9}R^8, -LNR^{9}R^{10}, -LC(O)N(R^9)$_2$, –LS(O)$_2$R^8, –LS(O)R^8, -LC(O)NR^{8}OH, -LNR^{9}C(O)R^8, -LNR^{9}C(O)OR^8, –LS(O)$_2$N(R^9)$_2$, -OLS(O)$_2$N(R^9)$_2$, -LNR^{9}S(O)$_2$R^8, -LC(O)NR^{9}LN(R^9)$_2$, -LP(O)(OR^8)$_2$, -LOP(O)(OR^8)$_2$, -LP(O)(OR^{10})$_2$ and -OLP(O)(OR^{10})$_2$.

[00020] In certain embodiments of such compounds of Formulas (I) or (I-A), Formulas (X-A) and (XI) to (XIV), R^7 is selected from H, C$_1$-C$_6$alkyl, aryl, heteroaryl, C$_3$-C$_8$cycloalkyl, and C$_3$-C$_8$heterocycloalkyl, wherein the C$_1$-C$_6$alkyl, aryl, heteroaryl, C$_3$-C$_8$cycloalkyl, and C$_3$-C$_8$heterocycloalkyl groups are each optionally substituted with 1-3 R^{13} groups and each R^{13} is independently selected from halogen, C$_1$-C$_6$haloalkyl, LR^8, LR^9, -LOR^8 and -OLR^8.

[00021] In certain embodiments of compounds of Formulas (I) or (I-A), Formulas (X-A) and (XI) to (XIV), have a structure of Formula (XV) or Formula (XVI):



Formula (XV)



Formula (XVI).

[00022] In certain embodiments of such compounds of Formulas (I) or (I-A), Formulas (X-A) and (XI) to (XVI), R^{13} is selected from -LR^9, -LOR^9, -OLR^9, -LR^{10}, -LOR^{10}, -OLR^{10}, -LR^8, -LOR^8, -OLR^8, -LSR^8, -LSR^{10}, -LC(O)R^8, -OLC(O)R^8, -LC(O)OR^8, -LC(O)R^{10}, -LOC(O)OR^8, -LC(O)NR^{9}R^{11}, -LC(O)NR^{9}R^8, -LN(R^9)$_2$, -LNR^{9}R^8, -LNR^{9}R^{10}, -LC(O)N(R^9)$_2$, –LS(O)$_2$R^8, -LS(O)R^8, -LC(O)NR^{8}OH, -LNR^{9}C(O)R^8, -LNR^{9}C(O)OR^8, –LS(O)$_2$N(R^9)$_2$, -OLS(O)$_2$N(R^9)$_2$, -LNR^{9}S(O)$_2$R^8, -LC(O)NR^{9}LN(R^9)$_2$, -LP(O)(OR^8)$_2$, -LOP(O)(OR^8)$_2$, -LP(O)(OR^{10})$_2$ and -OLP(O)(OR^{10})$_2$.

[00023] In certain embodiments of such compounds of Formulas (I) or (I-A), Formulas (X-A) and (XI) to (XVI), R^{10} is an aryl or a heteroaryl, wherein the aryl and heteroaryl groups are optionally substituted with 1 to 3 substituents selected from halogen, –R^8, -OR^8, and -N(R^9)$_2$.

[00024] In certain embodiments of such compounds of Formulas (I) or (I-A) Formulas (X-A) and (XI) to (XVI), R^{10} is phenyl optionally substituted with 1 to 3 substituents selected from halogen, –R^8, -OR^8, and -N(R^9)$_2$.

[00025] In certain embodiments of such compounds of Formulas (I) or (I-A), Formulas (X-

A) and (XI) to (XVI), R^8 is selected from H, C_1-C_6alkyl and C_1-C_6haloalkyl. In certain embodiments of the compounds of Formula XIII, XIV, XV or XVI, the compound is selected from: 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 2-(4-(dimethylamino)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine, and 2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine. Each of these compounds individually comprises a preferred embodiment of the compounds, compositions, and methods described herein.

[00026] In certain embodiments of the compounds, compositions and methods described herein, the compound of Formulas (I) is selected from 2-methylbenzo[f][1,7]naphthyridin-5-amine; 2-propylbenzo[f][1,7]naphthyridin-5-amine; 2-ethylbenzo[f][1,7]naphthyridin-5-amine; 2-(3-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-difluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; methyl 5-aminobenzo[f][1,7]naphthyridine-3-carboxylate; 5-amino-N-methylbenzo[f][1,7]naphthyridine-3-carboxamide; (5-aminobenzo[f][1,7]naphthyridin-3-yl)methanol; 8-phenylbenzo[f][1,7]naphthyridin-5-amine; 3-(ethoxymethyl)benzo[f][1,7]naphthyridin-5-amine; benzo[f][1,7]naphthyridine-3,5-diamine; benzo[f][1,7]naphthyridin-5-amine; methyl 5-aminobenzo[f][1,7]naphthyridine-8-carboxylate; 5-aminobenzo[f][1,7]naphthyridine-8-carboxylic acid; ethyl 5-aminobenzo[f][1,7]naphthyridine-8-carboxylate; (5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol; 5-aminobenzo[f][1,7]naphthyridine-3-carboxylic acid; 5-aminobenzo[f][1,7]naphthyridine-3-carbaldehyde; 2-(2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-chlorobenzo[f][1,7]naphthyridin-5-amine; ethyl 5-aminobenzo[f][1,7]naphthyridine-9-carboxylate; 8-methoxybenzo[f][1,7]naphthyridin-5-amine; 8-(methylsulfonyl)benzo[f][1,7]naphthyridin-5-amine; 8-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine; 8-fluorobenzo[f][1,7]naphthyridin-5-amine; 3-methoxybenzo[f][1,7]naphthyridin-5-amine; 3-butoxybenzo[f][1,7]naphthyridin-5-amine; 3-

(benzyloxy)benzo[f][1,7]naphthyridin-5-amine; 3-methylbenzo[f][1,7]naphthyridin-5-amine; 3-chlorobenzo[f][1,7]naphthyridin-5-amine; N3,N3-dimethylbenzo[f][1,7]naphthyridine-3,5-diamine; N3-butylbenzo[f][1,7]naphthyridine-3,5-diamine; 3-vinylbenzo[f][1,7]naphthyridin-5-amine; 3-ethylbenzo[f][1,7]naphthyridin-5-amine; 3-fluorobenzo[f][1,7]naphthyridin-5-amine; 2-phenethylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(naphthalen-1-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(naphthalen-2-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoic acid; 3-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoic acid; 2-(3-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (3-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol; 2-(4-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-butylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-butylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-propylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,5-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-propylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2,4,5-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,5-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-isopropylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-heptylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-isobutoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-((2-methoxyethoxy)methoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-phenoxyethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(tert-butyldimethylsilyloxy)ethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-phenylbutoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(allyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(3-phenylpropoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(heptan-4-yloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-methylpent-3-enyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-cyclohexylethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-isopropoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(3,3-dimethylbutoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(tert-butyldimethylsilyloxy)ethoxy)-2-

methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide; N-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide; N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-4-methylbenzenesulfonamide; 3-methyl-9-p-tolyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzonitrile; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-aminoethyl)-3-methylbenzamide; 8-methyl-2-(2-methyl-4-(1H-tetrazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; methyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoate; methyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetic acid; 6-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)hexan-1-ol; 7-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)heptanoic acid; 11-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)undecan-1-ol; ethyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)acetate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)acetic acid; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propanoic acid; 6-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)hexanoic acid; 8-methyl-2-(2-methyl-4-(methylthio)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(methylsulfonyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(hexyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-phenethoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(pentyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-methylpentyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(thiophen-3-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; (5-aminobenzo[f][1,7]naphthyridin-2-yl)methanol; 2-(3,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3,4-dimethylphenethyl)-8-

methylbenzo[f][1,7]naphthyridin-5-amine; 2-(3,5-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(benzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-nitroethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(aminomethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; N2,8-dimethylbenzo[f][1,7]naphthyridine-2,5-diamine; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-phenylethanol; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(4-methoxyphenyl)ethanol; 2-(biphenyl-2-yl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,6-dimethylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(5-methoxypyridin-2-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoic acid; 5-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-4-methylpyridin-2(1H)-one; 6-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)pyridin-3-ol; 8-methyl-2-(4-(trifluoromethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,3-dihydro-1H-inden-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,3-dihydro-1H-inden-5-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; (E)-3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylic acid; (E)-ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylate; 8-(prop-1-en-2-yl)benzo[f][1,7]naphthyridin-5-amine; 5-aminobenzo[f][1,7]naphthyridine-8-carbonitrile; (E)-8-(3-methylbut-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-methylprop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; (E)-8-(pent-1-enyl)benzo[f][1,7]naphthyridin-5-amine; (E)-8-styrylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-(2-cyclopropylvinyl)-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; 8-pentylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-(2-cyclopropylvinyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; 9-phenethylpyrido[1,2-c][1,7]naphthyridin-6-amine; methyl 5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridine-8-carboxylate; 8-nitrobenzo[f][1,7]naphthyridin-5-amine; 3-chloro-8-methylbenzo[f][1,7]naphthyridin-5-amine; methyl 5-amino-3-chlorobenzo[f][1,7]naphthyridine-8-carboxylate; methyl 5-amino-3-fluorobenzo[f][1,7]naphthyridine-8-carboxylate; 3-chloro-8-nitrobenzo[f][1,7]naphthyridin-5-amine; (5-amino-3-chlorobenzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-phenethylbenzo[f][1,7]naphthyridin-8-yl)methanol; 4-(2-(5-amino-8-fluorobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzaldehyde; 2-(4-(2-(5-amino-8-fluorobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzylamino)ethanol; 3-(4-(2-(5-amino-8-

fluorobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzylamino)propan-1-ol; 8-fluoro-2-(4-((2-methoxyethylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 3-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol; 2-(2-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-ethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-ethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(piperidin-1-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-tert-butylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(piperidin-1-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(3,5-dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-hydroxybenzimidamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzonitrile; 8-methyl-2-(4-(1-morpholinoethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-aminophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)guanidine; 8-methyl-2-(4-(1-(phenethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetonitrile; 2-(4-(piperidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzyl)piperidin-4-ol; 2-(4-(aminomethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-((ethylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-aminopropan-2-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-(1-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid; 8-methyl-2-(4-(1-(phenylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-ethyl-8-methylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)methanol; 8-methyl-2-propylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(1H-indol-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-ethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-phenoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-

dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol; 2-(2-(2,3-dihydrobenzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethanol; 3-methyl-9-phenyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine; 8-methylbenzo[f][1,7]naphthyridine-2,5-diamine; 1-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)propan-2-ol; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetonitrile; N-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetamide; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(2,4-dimethylphenyl)ethanol; 2-(2-(6-methoxy-4-methylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)butan-1-ol; methyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoate; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-1-ol; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-2-methylbutan-2-ol; 2-(4-(aminomethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (E)-ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylate; ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzyl)propane-1,3-diol; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoic acid; 5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridine-8-carbaldehyde; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoate; 8-methyl-2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-2-ol; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoic acid; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)methanol; 8-methyl-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 8-methyl-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; (E)-3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylic acid; ethyl 3-(5-amino-2-(4-methoxy-2-

methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoate; 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoic acid; 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propan-1-ol; 5-aminobenzo[f][1,7]naphthyridin-8-ol; 5-aminobenzo[f][1,7]naphthyridine-8-carbaldehyde; 1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanol; 1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanone; 8-isopropylbenzo[f][1,7]naphthyridin-5-amine; 8-vinylbenzo[f][1,7]naphthyridin-5-amine; 8-ethylbenzo[f][1,7]naphthyridin-5-amine; 8-(methoxymethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; benzo[f][1,7]naphthyridine-5,8-diamine; 8-(aminomethyl)benzo[f][1,7]naphthyridin-5-amine; 3-fluoro-8-methylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-3-fluorobenzo[f][1,7]naphthyridin-8-yl)methanol; 3-chlorobenzo[f][1,7]naphthyridine-5,8-diamine; 3-fluorobenzo[f][1,7]naphthyridine-5,8-diamine; 8-isobutylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-(prop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 8-propylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)benzo[f][1,7]naphthyridin-5-amine; 8-phenethylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(4-bromophenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 2-(4-methoxy-2-methylphenethyl)-8-pentylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; (2-(2-(1H-indol-5-yl)ethyl)-5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol; methyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,3-dimethylbenzamide; N-(2-acetamidoethyl)-4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide; 2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,N,3-trimethylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-hydroxyethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-3-methylbenzamide; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-

methylphenyl)(pyrrolidin-1-yl)methanone; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(diethylamino)ethyl)-3-methylbenzamide; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(4-ethylpiperazin-1-yl)methanone; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(piperazin-1-yl)methanone; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methyl-N-(2-(pyrrolidin-1-yl)ethyl)benzamide; 4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N-methylbenzamide; 2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 2-(4-butoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(biphenyl-4-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-((1,3-dihydroisobenzofuran-1-yl)methyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-methylallyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(isopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl propyl carbonate; ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoate; 2-(4-(cyclopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(cyclobutylmethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-1-phenylethanone; 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)ethanol; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-N,N-dimethylacetamide; 8-methyl-2-(2-methyl-4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethanol; diethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonate; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonic acid; 2-(4-butoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol; 2-(2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethanol; ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoate; 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol; 4-(2-(5-amino-8-

methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl ethyl carbonate; methyl 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoate; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoic acid; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)butanoic acid; 2-(4-(isopentyloxy)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl hexyl carbonate; 2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; diethyl 3-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)propylphosphonate; diethyl 3-(2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethoxy)propylphosphonate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl dimethylsulfamate; (5-amino-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 2-(4-(dimethylamino)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone; 2-(4-((dimethylamino)methyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(1-(dimethylamino)ethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone oxime; 8-methyl-2-(4-((methylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzylamino)ethanol; 8-methyl-2-(4-(pyrrolidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3,4-dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)ethanol; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanol; 8-methyl-2-(4-(oxazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propanenitrile; (2R)-2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propan-1-ol; 8-methyl-2-(4-(1-(piperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; ((2S)-1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidin-2-yl)methanol; N1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N2,N2-dimethylethane-1,2-diamine; 3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-

yl)ethyl)phenyl)ethylamino)propanoic acid; 8-methyl-2-(4-(1-(4-methylpiperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; N2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N1,N1-dimethylpropane-1,2-diamine; 8-methyl-2-(4-(1-(2-(pyridin-4-yl)ethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; N1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N2,N2-diethylethane-1,2-diamine; 2-(4-(dimethylamino)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid; 4-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)phenol; 1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2 yl)ethyl)phenyl)ethyl)pyrrolidin-3-ol, and 2-(4-(2-aminopropan-2-yl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine.

[00027] In certain embodiments of the compounds, compositions and methods described herein, the compound of Formulas (I-A) is selected from the following compounds and their pharmaceutically acceptable salts:

2-methylbenzo[f][1,7]naphthyridin-5-amine; 2-propylbenzo[f][1,7]naphthyridin-5-amine; 2-ethylbenzo[f][1,7]naphthyridin-5-amine; 2-(3-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; methyl 5-aminobenzo[f][1,7]naphthyridine-3-carboxylate; (5-aminobenzo[f][1,7]naphthyridin-3-yl)methanol; benzo[f][1,7]naphthyridin-5-amine; (5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol; 2-(2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-chlorobenzo[f][1,7]naphthyridin-5-amine; ethyl 5-aminobenzo[f][1,7]naphthyridine-9-carboxylate; 8-methoxybenzo[f][1,7]naphthyridin-5-amine; 8-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine; 8-fluorobenzo[f][1,7]naphthyridin-5-amine; 3-methylbenzo[f][1,7]naphthyridin-5-amine; 3-fluorobenzo[f][1,7]naphthyridin-5-amine; 2-phenethylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(naphthalen-1-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(naphthalen-2-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoic acid; 3-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoic acid; 2-(3-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (3-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol; 2-(4-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-

butylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-butylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-propylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,5-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-propylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2,4,5-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,5-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-isopropylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-heptylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-isobutoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-((2-methoxyethoxy)methoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-phenoxyethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-phenylbutoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(allyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(3-phenylpropoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(heptan-4-yloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-methylpent-3-enyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-cyclohexylethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-isopropoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(3,3-dimethylbutoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide; N-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide; N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-4-methylbenzenesulfonamide; 3-methyl-9-p-tolyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzonitrile; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-aminoethyl)-3-methylbenzamide; 8-methyl-2-(2-methyl-4-(1H-tetrazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; methyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoate; methyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoic

acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetic acid; 6-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)hexan-1-ol; 7-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)heptanoic acid; 11-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)undecan-1-ol; ethyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)acetate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)acetic acid; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propanoic acid; 6-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)hexanoic acid; 8-methyl-2-(2-methyl-4-(methylthio)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(methylsulfonyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(hexyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-phenethoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(pentyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-methylpentyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(thiophen-3-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; (5-aminobenzo[f][1,7]naphthyridin-2-yl)methanol; 2-(3,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3,4-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(3,5-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(benzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-nitroethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(aminomethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; N^2,8-dimethylbenzo[f][1,7]naphthyridine-2,5-diamine; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-phenylethanol; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(4-methoxyphenyl)ethanol; 2-(biphenyl-2-yl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,6-dimethylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(5-methoxypyridin-2-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoic acid; 5-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-4-methylpyridin-2(1H)-one; 6-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)pyridin-3-ol; 8-methyl-2-(4-(trifluoromethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,3-dihydro-1H-inden-5-

yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,3-dihydro-1H-inden-5-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; (E)-3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylic acid; (E)-ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylate; (E)-8-(2-cyclopropylvinyl)-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; 8-pentylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-(2-cyclopropylvinyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-2-phenethylbenzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 3-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol; 2-(2-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-ethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-ethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(piperidin-1-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-tert-butylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(piperidin-1-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(3,5-dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-hydroxybenzimidamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzonitrile; 8-methyl-2-(4-(1-morpholinoethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-aminophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)guanidine; 8-methyl-2-(4-(1-(phenethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetonitrile; 2-(4-(piperidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzyl)piperidin-4-ol; 2-(4-(aminomethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-((ethylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-aminopropan-2-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-(1-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid; 8-methyl-2-(4-(1-(phenylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-ethyl-8-

methylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)methanol; 8-methyl-2-propylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(1H-indol-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-ethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-phenoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol; 2-(2-(2,3-dihydrobenzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethanol; 3-methyl-9-phenyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine; 8-methylbenzo[f][1,7]naphthyridine-2,5-diamine; 1-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)propan-2-ol; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetonitrile; N-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetamide; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(2,4-dimethylphenyl)ethanol; 2-(2-(6-methoxy-4-methylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)butan-1-ol; methyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoate; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-1-ol; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-2-methylbutan-2-ol; 2-(4-(aminomethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (E)-ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylate; ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzyl)propane-1,3-diol; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoic acid; 5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridine-8-carbaldehyde; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoate; 8-methyl-2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-2-ol; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoic acid; (4-(2-(5-amino-8-

methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)methanol; 8-methyl-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 8-methyl-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; (E)-3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylic acid; ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoate; 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoic acid; 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propan-1-ol; 5-aminobenzo[f][1,7]naphthyridin-8-ol; 5-aminobenzo[f][1,7]naphthyridine-8-carbaldehyde; 1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanol; 1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanone; 8-isopropylbenzo[f][1,7]naphthyridin-5-amine; 8-vinylbenzo[f][1,7]naphthyridin-5-amine; 8-ethylbenzo[f][1,7]naphthyridin-5-amine; 8-(methoxymethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; benzo[f][1,7]naphthyridine-5,8-diamine; 8-(aminomethyl)benzo[f][1,7]naphthyridin-5-amine; 3-fluoro-8-methylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-3-fluorobenzo[f][1,7]naphthyridin-8-yl)methanol; 3-chlorobenzo[f][1,7]naphthyridine-5,8-diamine; 3-fluorobenzo[f][1,7]naphthyridine-5,8-diamine; 8-isobutylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-(prop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 8-propylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)benzo[f][1,7]naphthyridin-5-amine; 8-phenethylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(4-bromophenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 2-(4-methoxy-2-methylphenethyl)-8-pentylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; (2-(2-(1H-indol-5-yl)ethyl)-5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol; methyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,3-dimethylbenzamide; N-(2-acetamidoethyl)-4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide; 2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide; 4-(2-(5-amino-8-

methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,N,3-trimethylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-hydroxyethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-3-methylbenzamide; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(pyrrolidin-1-yl)methanone; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(diethylamino)ethyl)-3-methylbenzamide; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(4-ethylpiperazin-1-yl)methanone; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(piperazin-1-yl)methanone; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methyl-N-(2-(pyrrolidin-1-yl)ethyl)benzamide; 4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N-methylbenzamide; 2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 2-(4-butoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(biphenyl-4-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-((1,3-dihydroisobenzofuran-1-yl)methyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-methylallyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(isopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl propyl carbonate; ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoate; 2-(4-(cyclopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(cyclobutylmethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-1-phenylethanone; 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)ethanol; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-N,N-dimethylacetamide; 8-methyl-2-(2-methyl-4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethanol; diethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonate; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonic acid; 2-(4-butoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol; 2-(2-(4-(2-(5-

aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethanol; ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoate; 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl ethyl carbonate; methyl 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoate; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoic acid; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)butanoic acid; 2-(4-(isopentyloxy)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl hexyl carbonate; 2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; diethyl 3-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)propylphosphonate; diethyl 3-(2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethoxy)propylphosphonate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl dimethylsulfamate; (5-amino-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 2-(4-(dimethylamino)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone; 2-(4-((dimethylamino)methyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(1-(dimethylamino)ethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone oxime; 8-methyl-2-(4-((methylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzylamino)ethanol; 8-methyl-2-(4-(pyrrolidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3,4-dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)ethanol; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanol; 8-methyl-2-(4-(oxazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propanenitrile; (2R)-2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propan-1-ol; 8-methyl-2-(4-(1-

(piperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; ((2S)-1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidin-2-yl)methanol; N^1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^2,N^2-dimethylethane-1,2-diamine; 3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propanoic acid; 8-methyl-2-(4-(1-(4-methylpiperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; N^2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^1,N^1-dimethylpropane-1,2-diamine; 8-methyl-2-(4-(1-(2-(pyridin-4-yl)ethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; N^1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^2,N^2-diethylethane-1,2-diamine; 2-(4-(dimethylamino)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid; 4-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)phenol; 1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2 yl)ethyl)phenyl)ethyl)pyrrolidin-3-ol; and 2-(4-(2-aminopropan-2-yl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine.

[00028] In certain embodiments of compounds of Formula (XVI), or a pharmaceutically acceptable salt thereof, each R^4, R^A and R^{13} is independently selected from H, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH_2OH$, $-OCH_3$, $-COOCH_3$, F, Cl, Br, $-CH_2OCH_3$, $-COOCH_2CH_3$, $CH_2OCH_2CH_3$, $-N(CH_3)_2$, $-((O(CH_2)_2)_{2-4}OH$, $-O(CH_2)_{2-4}$-OH, $-O(CH_2)_{2-4}(PO_3H_2)$, $-O(CH_2)_{2-4}$-COOH, $-O(CH_2)_{2-4}CH(CH_3)_2$, C_2-C_6 alkyl substituted with 1-3 substituents selected from –OH, $-CH_3$, cyclopropyl, $-O(CH_2)_{2-4}$-COOH, $-O(CH_2)_{2-4}(PO_3H_2)$, -COOH, $COOCH_3$, and $-COOCH_2CH_3$. In other embodiments of compounds of Formula (XVI), R^4 is H. In other embodiments such compounds of Formula (XVI), have one to three R^{13} groups. In other embodiments of such compounds of Formula (XVI), R^A is H or Me. In other embodiments such compounds of Formula (XVI), have two R^{13} groups selected from the group consisting of $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH_2OH$, $-OCH_3$, $-COOCH_3$, $-COOCH_2CH_3$, F, Cl, Br, $-CH_2OCH_3$, $CH_2OCH_2CH_3$, $-N(CH_3)_2$, $-((O(CH_2)_2)_{2-4}OH$, $-O(CH_2)_{2-4}$-OH, $-O(CH_2)_{2-4}(PO_3H_2)$, $-O(CH_2)_{2-4}$-COOH, $-O(CH_2)_{2-4}CH(CH_3)_2$, C_2-C_6 alkyl substituted with 1-3 substituents selected from –OH, $-CH_3$, cyclopropyl, $-O(CH_2)_{2-4}$-COOH, $-O(CH_2)_{2-4}(PO_3H_2)$, -COOH, $COOCH_3$, and $-COOCH_2CH_3$. In other embodiments such compounds of Formula (XVI) are selected from: 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2,4-

dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 2-(4-(dimethylamino)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine, and 2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine.

[00029] Another aspect provided herein are pharmaceutical compositions that include a therapeutically effective amount of a compound of Formula (I) described above and a pharmaceutically acceptable carrier.

[00030] In certain embodiments of this aspect, the pharmaceutical composition is formulated for intravenous administration, intravitrial administration, intramuscular administration, oral administration, rectal administration inhalation, nasal administration, topical administration, ophthalmic administration or otic administration. In other embodiments, the pharmaceutical compositions are in the form of a tablet, a pill, a capsule, a liquid, an inhalant, a nasal spray solution, a suppository, a solution, an emulsion, an ointment, eye drop or ear drop. In other embodiments, such pharmaceutical compositions further include one or more additional therapeutic agents.

[00031] Another aspect provided herein are medicaments for treating a disease or disorder in a patient where modulation of a TLR receptor is implicated and such medicaments include a therapeutically effective amount of a compound of Formula (I). In certain embodiments of such medicaments, the TLR receptor is TLR7. In other embodiments of such medicaments, the TLR receptor is TLR8. In certain embodiments of such medicaments, the compound is a TLR receptor agonist. In certain embodiments of such medicaments, the compound is a TLR7 receptor agonist. In certain embodiments of such medicaments, the compound is a TLR8 receptor agonist.

[00032] Another aspect provided herein is the use of a compound of Formula (I) in the manufacture of a medicament for treating a disease or disorder in a patient where modulation of a TLR receptor is implicated.

[00033] Another aspect provided herein includes methods for modulating a TLR receptor, wherein the method include administering to a system or a subject in need thereof, a therapeutically effective amount of a compound of Formula (I), or pharmaceutically acceptable salts or pharmaceutical compositions thereof, thereby modulating the TLR receptor. In certain embodiments of such methods, the TLR receptor is TLR7. In other embodiments of such methods, the TLR receptor is TLR8. In certain embodiments of such methods, the compound is a TLR receptor agonist. In certain embodiments of such methods, the compound is a TLR7 receptor

agonist. In certain embodiments of such methods, the compound is a TLR8 receptor agonist. In certain embodiments of such methods, the methods include administering the compound to a cell or tissue system or to a human or animal subject.

[00034] In certain embodiments of the methods provided herein for the treatment of a subject for a specified condition or disorder where a TLR is implicated, such methods further comprise an optional step of identifying a subject in need of such treatment.

[00035] Another aspect provided herein includes methods for treating a disease or disorder where modulation of TLR receptor is implicated, wherein the method includes administering to a system or subject in need of such treatment an effective amount of a compound of Formula (I), or pharmaceutically acceptable salts or pharmaceutical compositions thereof, thereby treating the disease or disorder. In certain embodiments of such methods, the TLR receptor is TLR7. In other embodiments of such methods, the TLR receptor is TLR8. In certain embodiments of such methods, the compound is a TLR receptor agonist. In certain embodiments of such methods, the compound is a TLR7 receptor agonist. In certain embodiments of such methods, the compound is a TLR8 receptor agonist. In certain embodiments of such methods, the methods include administering the compound to a cell or tissue system or to a human or animal subject.

[00036] In certain embodiments of such methods, the disease or condition is an infectious disease, an inflammatory disease, a respiratory disease, a dermatological disease or an autoimmune disease. In certain embodiments of such methods, the disease or condition is asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohns disease, bronchitis, dermatitis, actinic keratosis, basal cell carcinoma, allergic rhinitis, psoriasis, scleroderma, urticaria, rheumatoid arthritis, multiple sclerosis, cancer, breast cancer, HIV or lupus.

[00037] Another aspect provided herein includes methods for treating a cell-proliferative disease, comprising administering to a system or subject in need of such treatment an effective amount of a compound of Formula (I), or pharmaceutically acceptable salts or pharmaceutical compositions thereof; wherein the cell-proliferative disease is lymphoma, osteosarcoma, melanoma, or a tumor of breast, renal, prostate, colorectal, thyroid, ovarian, pancreatic, neuronal, lung, uterine or gastrointestinal tumor.

[00038] Another aspect provided herein are pharmaceutical composition that include a compound of Formula (I) of (I-A), an antigen and a pharmaceutically acceptable carrier, wherein such pharmaceutical compositions are immunogenic compositions, and the compound is an

immune potentiator and is present in an amount effective to enhance an immune response to the antigen, in a subject receiving the composition. In certain embodiments, such pharmaceutical compositions, further includes one or more immunoregulatory agents. In certain embodiments, the one or more immunoregulatory agents include one or more adjuvants. In certain embodiments, such adjuvants are selected from adjuvants that are a mineral-containing composition, an oil emulsion, a saponin formulation, a virosome, a virus-like particle, a bacterial derivative, a microbial derivative, a human immunomodulator, a bioadhesive, a mucoadhesive, a microparticle, a liposome, a polyoxyethylene ether formulation, a polyoxyethylene ester formulation, a polyphosphazene, a muramyl peptide, or an imidazoquinolone compound. In certain embodiments, the adjuvant is an oil emulsion. In certain embodiments the immunogenic compositions are useful as vaccines, and the compound is present in an amount sufficient to produce an immunostimulatory effect upon administration.

[00039] Another aspect provided herein includes methods for enhancing the effectiveness of an immunogenic composition, comprising adding an effective amount of a compound Formula (I) or (I-A) to the immunogenic composition.

[00040] Another aspect provided herein are immunogenic compositions comprising a compound of Formula (I-A), and an antigen, wherein the amount of the compound is an amount effective to enhance an immune response to the antigen in a subject to whom the composition is administered. In certain embodiments of such immunogenic compositions the antigen is a bacterial antigen. In certain embodiments of such immunogenic compositions the bacterial antigen is an antigen of a strain of *Neisseria meningitides*. In other embodiments of such immunogenic compositions the antigen is a viral antigen or a fungal antigen. In other embodiments such immunogenic compositions further comprising an additional adjuvant. In certain embodiments of such immunogenic compositions the antigen is a polypeptide. In certain embodiments of such immunogenic compositions the polypeptide has at least 85% identity to a sequence selected from the group consisting of SEQ ID NOs: 1-6 provided herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[00041] FIG. 1 shows the serum bactericidal antibody ("SBA") titer of certain compounds disclosed herein to enhance the immune response to a bacterial antigen. The dose of the compound in μg is indicated on the left, and the fold-change over the response elicited with MF59/3MenB is shown to the right of each bar.The results are compared to "CpG" (CpG oligonucleotide), R848, and Immiquimod (ImiQ).

[00042] FIG. 2 shows the serum bactericidal antibody ("SBA") titer of compound 47 disclosed herein to enhance the immune response to a bacterial antigen. The dose of the compound in μg is indicated on the left, and the fold-change over the response elicited with MF59/3MenB is shown to the right of each bar.The results are compared to "CpG" (CpG oligonucleotide), R848, and Immiquimod (ImiQ).

[00043] FIG. 3 shows the serum bactericidal antibody ("SBA") titer of compound 47 disclosed herein to enhance the immune response to a bacterial antigen. The dose of the compound in μg is indicated on the left, and the fold-change over the response elicited with MF59/3MenB is shown to the right of each bar.The results are compared to "CpG" (CpG oligonucleotide), R848, and Immiquimod (ImiQ).

[00044] FIG. 4 shows the serum bactericidal antibody ("SBA") titer of compound 169 disclosed herein to enhance the immune response to a bacterial antigen. The dose of the compound in μg is indicated on the left, and the fold-change over the response elicited with MF59/3MenB is shown to the right of each bar.The results are compared to "CpG" (CpG oligonucleotide), R848, and Immiquimod (ImiQ).

[00045] FIG. 5 is a compilation of the data shown in Figures 1-4.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[00046] The term "alkenyl," as used herein, refers to a partially unsaturated branched or straight chain hydrocarbon having at least one carbon-carbon double bond. Atoms oriented about the double bond are in either the cis (Z) or trans (E) conformation. An alkenyl group can be optionally substituted. As used herein, the terms "C_2-C_3alkenyl", "C_2-C_4alkenyl", "C_2-C_5alkenyl", "C_2-C_6alkenyl", "C_2-C_7alkenyl", and "C_2-C_8alkenyl" refer to an alkenyl group containing at least 2, and at most 3, 4, 5, 6, 7 or 8 carbon atoms, respectively. If not otherwise specified, an alkenyl group generally is a C_2-C_6 alkenyl. Non-limiting examples of alkenyl groups, as used herein, include ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl and the like.

[00047] The term "alkenylene," as used herein, refers to a partially unsaturated branched or straight chain divalent hydrocarbon radical derived from an alkenyl group. An alkenylene group can be optionally substituted. As used herein, the terms "C_2-C_3alkenylene", "C_2-C_4alkenylene", "C_2-C_5alkenylene", "C_2-C_6alkenylene", "C_2-C_7alkenylene", and "C_2-C_8alkenylene" refer to an alkenylene group containing at least 2, and at most 3, 4, 5, 6, 7 or 8 carbon atoms respectively. If not otherwise specified, an alkenylene group generally is a C_1-C_6 alkenylene.Non-limiting

examples of alkenylene groups as used herein include, ethenylene, propenylene, butenylene, pentenylene, hexenylene, heptenylene, octenylene, nonenylene, decenylene and the like.

[00048] The term "alkyl," as used herein, refers to a saturated branched or straight chain hydrocarbon. An alkyl group can be optionally substituted. As used herein, the terms "C_1-C_3alkyl", "C_1-C_4alkyl", "C_1-C_5alkyl", "C_1-C_6alkyl", "C_1-C_7alkyl" and "C_1-C_8alkyl" refer to an alkyl group containing at least 1, and at most 3, 4, 5, 6, 7 or 8 carbon atoms, respectively. If not otherwise specified, an alkyl group generally is a C_1-C_6 alkyl. Non-limiting examples of alkyl groups as used herein include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, hexyl, heptyl, octyl, nonyl, decyl and the like.

[00049] The term "alkylene," as used herein, refers to a saturated branched or straight chain divalent hydrocarbon radical derived from an alkyl group. An alkylene group can be optionally substituted. As used herein, the terms "C_1-C_3alkylene", "C_1-C_4alkylene", "C_1-C_5alkylene", "C_1-C_6alkylene", "C_1-C_7alkylene" and "C_1-C_8alkylene" refer to an alkylene group containing at least 1, and at most 3, 4, 5, 6, 7 or 8 carbon atoms respectively. If not otherwise specified, an alkylene group generally is a C_1-C_6 alkylene. Non-limiting examples of alkylene groups as used herein include, methylene, ethylene, n-propylene, isopropylene, n-butylene, isobutylene, sec-butylene, t-butylene, n-pentylene, isopentylene, hexylene and the like.

[00050] The term "alkynyl," as used herein, refers to a partially unsaturated branched or straight chain hydrocarbon having at least one carbon-carbon triple bond. An alkynyl group can be optionally substituted. As used herein, the terms "C_2-C_3alkynyl", "C_2-C_4alkynyl", "C_2-C_5alkynyl", "C_2-C_6alkynyl", "C_2-C_7alkynyl", and "C_2-C_8alkynyl" refer to an alkynyl group containing at least 2, and at most 3, 4, 5, 6, 7 or 8 carbon atoms, respectively. If not otherwise specified, an alkynyl group generally is a C_2-C_6 alkynyl. Non-limiting examples of alkynyl groups, as used herein, include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl and the like.

[00051] The term "alkynylene," as used herein, refers to a partially unsaturated branched or straight chain divalent hydrocarbon radical derived from an alkynyl group. An alkynylene group can be optionally substituted. As used herein, the terms "C_2-C_3alkynylene", "C_2-C_4alkynylene", "C_2-C_5alkynylene", "C_2-C_6alkynylene", "C_2-C_7alkynylene", and "C_2-C_8alkynylene" refer to an alkynylene group containing at least 2, and at most 3, 4, 5, 6, 7 or 8 carbon atoms respectively. If not otherwise specified, an alkynylene group generally is a C_2-C_6 alkynylene. Non-limiting examples of alkynylene groups as used herein include, ethynylene, propynylene, butynylene, pentynylene, hexynylene, heptynylene, octynylene, nonynylene, decynylene and the like.

[00052] The term "alkoxy," as used herein, refers to the group $-OR_a$, where R_a is an alkyl group as defined herein. An alkoxy group can be optionally substituted. As used herein, the terms "C_1-C_3alkoxy", "C_1-C_4alkoxy", "C_1-C_5alkoxy", "C_1-C_6alkoxy", "C_1-C_7alkoxy" and "C_1-C_8alkoxy" refer to an alkoxy group wherein the alkyl moiety contains at least 1, and at most 3, 4, 5, 6, 7 or 8, carbon atoms. Non-limiting examples of alkoxy groups, as used herein, include methoxy, ethoxy, n-propoxy, isopropoxy, n-butyloxy, t-butyloxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, decyloxy and the like.

[00053] The term "aryl," as used herein, refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. An aryl group can be optionally substituted. Non-limiting examples of aryl groups, as used herein, include phenyl, naphthyl, fluorenyl, indenyl, azulenyl, anthracenyl and the like.

[00054] The term "arylene," as used means a divalent radical derived from an aryl group. An arylene group can be optionally substituted.

[00055] The term "cyano," as used herein, refers to a -CN group.

[00056] The term "cycloalkyl," as used herein, refers to a saturated or partially unsaturated, monocyclic, fused bicyclic, fused tricyclic or bridged polycyclic ring assembly. As used herein, the terms "C_3-C_5 cycloalkyl", "C_3-C_6 cycloalkyl", "C_3-C_7 cycloalkyl", "C_3-C_8 cycloalkyl, "C_3-C_9 cycloalkyl and "C_3-C_{10} cycloalkyl refer to a cycloalkyl group wherein the saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly contain at least 3, and at most 5, 6, 7, 8, 9 or 10, carbon atoms. A cycloalkyl group can be optionally substituted. Non-limiting examples of cycloalkyl groups, as used herein, include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclopentenyl, cyclohexenyl, decahydronaphthalenyl, 2,3,4,5,6,7-hexahydro-1H-indenyl and the like.

[00057] The term "halogen," as used herein, refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I).

[00058] The term "halo," as used herein, refers to the halogen radicals: fluoro (-F), chloro (-Cl), bromo (-Br), and iodo (-I).

[00059] The terms "haloalkyl" or "halo-substituted alkyl," as used herein, refers to an alkyl group as defined herein, substituted with one or more halogen groups, wherein the halogen groups are the same or different. A haloalkyl group can be optionally substituted. Non-limiting examples of such branched or straight chained haloalkyl groups, as used herein, include methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl substituted with one or more halogen groups, wherein the

halogen groups are the same or different, including, but not limited to, trifluoromethyl, pentafluoroethyl, and the like.

[00060] The terms "haloalkenyl" or "halo-substituted alkenyl," as used herein, refers to an alkenyl group as defined herein, substituted with one or more halogen groups, wherein the halogen groups are the same or different. A haloalkenyl group can be optionally substituted. Non-limiting examples of such branched or straight chained haloalkenyl groups, as used herein, include ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl and the like substituted with one or more halogen groups, wherein the halogen groups are the same or different.

[00061] The terms "haloalkynyl" or "halo-substituted alkynyl," as used herein, refers to an alkynyl group as defined above, substituted with one or more halogen groups, wherein the halogen groups are the same or different. A haloalkynyl group can be optionally substituted. Non-limiting examples of such branched or straight chained haloalkynyl groups, as used herein, include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, and the like substituted with one or more halogen groups, wherein the halogen groups are the same or different.

[00062] The term "haloalkoxy," as used herein, refers to an alkoxy group as defined herein, substituted with one or more halogen groups, wherein the halogen groups are the same or different. A haloalkoxy group can be optionally substituted. Non-limiting examples of such branched or straight chained haloalkynyl groups, as used herein, include methoxy, ethoxy, n-propoxy, isopropoxy, n-butyloxy, t-butyloxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, decyloxy and the like, substituted with one or more halogen groups, wherein the halogen groups are the same or different.

[00063] The term "heteroalkyl," as used herein, refers to an alkyl group as defined herein wherein one or more carbon atoms are independently replaced by one or more of oxygen, sulfur, nitrogen, or combinations thereof.

[00064] The term "heteroaryl," as used herein, refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms selected from nitrogen, oxygen and sulfur, and wherein each ring in the system contains 3 to 7 ring members. A heteroaryl group may contain one or more substituents. A heteroaryl group can be optionally substituted. Non-limiting examples of heteroaryl groups, as used herein, include benzofuranyl, benzofurazanyl, benzoxazolyl, benzopyranyl, benzthiazolyl, benzothienyl, benzazepinyl, benzimidazolyl, benzothiopyranyl, benzo[1,3]dioxole, benzo[b]furyl, benzo[b]thienyl, cinnolinyl, furazanyl, furyl, furopyridinyl, imidazolyl, indolyl, indolizinyl, indolin-2-one, indazolyl,

isoindolyl, isoquinolinyl, isoxazolyl, isothiazolyl, 1,8-naphthyridinyl, oxazolyl, oxaindolyl, oxadiazolyl, pyrazolyl, pyrrolyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinoxalinyl, quinolinyl, quinazolinyl, 4H-quinolizinyl, thiazolyl, thiadiazolyl, thienyl, triazinyl,triazolyl and tetrazolyl.

[00065] The term "heterocycloalkyl," as used herein, refers to a cycloalkyl, as defined herein, wherein one or more of the ring carbons are replaced by a moiety selected from -O-, -N=, -NR-, -C(O)-, -S-, -S(O) - or -S(O)2-, wherein R is hydrogen, C_1-C_4alkyl or a nitrogen protecting group, with the proviso that the ring of said group does not contain two adjacent O or S atoms. A heterocycloalkyl group can be optionally substituted. Non-limiting examples of heterocycloalkyl groups, as used herein, include morpholino, pyrrolidinyl, pyrrolidinyl-2-one, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, 2H-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, 1,3-dioxolanyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, 1,4-dioxanyl, 1,4-dithianyl, thiomorpholinyl, azepanyl, hexahydro-1,4-diazepinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, thioxanyl, azetidinyl, oxetanyl, thietanyl, oxepanyl, thiepanyl, 1,2,3,6-tetrahydropyridinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, and 3-azabicyclo[4.1.0]heptanyl.

[00066] The term "heteroatom," as used herein, refers to one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon.

[00067] The term "hydroxyl," as used herein, refers to the group -OH.

[00068] The term "hydroxyalkyl," as used herein refers to an alkyl group as defined herein substituted with one or more hydroxyl group. Non-limiting examples of branched or straight chained "C_1-C_6 hydroxyalkyl groups as used herein include methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl groups substituted with one or more hydroxyl groups.

[00069] The term "isocyanato," as used herein, refers to a –N=C=O group.

[00070] The term "isothiocyanato," as used herein, refers to a –N=C=S group.

[00071] The term "mercaptyl," as used herein, refers to an (alkyl)S- group.

[00072] The term "optionally substituted," as used herein, means that the referenced group may or may not be substituted with one or more additional group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, hydroxyl, alkoxy, mercaptyl, cyano, halo, carbonyl, thiocarbonyl, isocyanato, thiocyanato, isothiocyanato, nitro, perhaloalkyl, perfluoroalkyl, and amino, including mono- and di-substituted amino groups,

and the protected derivatives thereof. Non-limiting examples of optional substituents include, halo, –CN, =O, =N-OH, =N-OR, =N-R, –OR, -C(O)R, -C(O)OR, -OC(O)R, -OC(O)OR, -C(O)NHR, -$C(O)NR_2$, -OC(O)NHR, -$OC(O)NR_2$, -SR-, -S(O)R, -$S(O)_2R$, -NHR, -$N(R)_2$, -NHC(O)R, –NRC(O)R, -NHC(O)OR, -NRC(O)OR, $S(O)_2NHR$, –$S(O)_2N(R)_2$, -$NHS(O)_2NR_2$, -$NRS(O)_2NR_2$, -$NHS(O)_2R$, -$NRS(O)_2R$, C_1-C_8alkyl, C_1-C_8alkoxy, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, halo-substituted C_1-C_8alkyl, and halo-substituted C_1-C_8alkoxy, where each R is independently selected from H, halo, C_1-C_8alkyl, C_1-C_8alkoxy, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, halo-substituted C_1-C_8alkyl, and halo-substituted C_1-C_8alkoxy. The placement and number of such substituent groups is done in accordance with the well-understood valence limitations of each group, for example =O is a suitable substituent for an alkyl group but not for an aryl group.

[00073] The term "solvate," as used herein, refers to a complex of variable stoichiometry formed by a solute (by way of example, a compound of Formula (I), or a salt thereof, as described herein) and a solvent. Non-limiting examples of a solvent are water, acetone, methanol, ethanol and acetic acid.

[00074] The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[00075] The term "administration" or "administering" of the subject compound means providing a compound of Formula (I), a pharmaceutically acceptable salt, a pharmaceutically acceptable solvate, or prodrug thereof to a subject in need of treatment.

[00076] The term "cancer," as used herein refers to an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread). The types of cancer include, but is not limited to, solid tumors (such as those of the bladder, bowel, brain, breast, endometrium, heart, kidney, lung, lymphatic tissue (lymphoma), ovary, pancreas or other endocrine organ (thyroid), prostate, skin (melanoma) or hematological tumors (such as the leukemias).

[00077] The term "carrier," as used herein, refers to chemical compounds or agents that facilitate the incorporation of a compound described herein into cells or tissues.

[00078] The terms "co-administration" or "combined administration" or the like as used herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

[00079] The term "dermatological disorder," as used herein refers to a skin disorder. Such

dermatological disorders include, but are not limited to, proliferative or inflammatory disorders of the skin such as, atopic dermatitis, bullous disorders, collagenoses, contact dermatitis eczema, Kawasaki Disease, rosacea, Sjogren-Larsso Syndrome, actinic keratosis, basal cell carcinoma and urticaria.

[00080] The term "diluent," as used herein, refers to chemical compounds that are used to dilute a compound described herein prior to delivery. Diluents can also be used to stabilize compounds described herein.

[00081] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of a compound described herein being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study.

[00082] The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[00083] The terms "fibrosis" or "fibrosing disorder," as used herein, refers to conditions that follow acute or chronic inflammation and are associated with the abnormal accumulation of cells and/or collagen and include but are not limited to fibrosis of individual organs or tissues such as the heart, kidney, joints, lung, or skin, and includes such disorders as idiopathic pulmonary fibrosis and cryptogenic fibrosing alveolitis.

[00084] The term "iatrogenic," as used herein, means a condition, disorder, or disease created or worsened by medical or surgical therapy.

[00085] The term "immunologically effective amount," as used herein, means that the administration of a sufficient amount to an individual, either in a single dose or as part of a series, that is effective for treatment or prevention of an immunological disease or disorder. This amount varies depending upon the health and physical condition of the individual to be treated, age, the taxonomic group of individual to be treated (e.g. non-human primate, primate, etc.), the capacity

of the individual's immune system to synthesize antibodies, the degree of protection desired, the formulation of the vaccine, the treating doctor's assessment of the medical situation, and other relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials.

[00086] The term "inflammatory disorders," as used herein, refers to those diseases or conditions that are characterized by one or more of the signs of pain (dolor, from the generation of noxious substances and the stimulation of nerves), heat (calor, from vasodilatation), redness (rubor, from vasodilatation and increased blood flow), swelling (tumor, from excessive inflow or restricted outflow of fluid), and loss of function (functio laesa, which may be partial or complete, temporary or permanent). Inflammation takes many forms and includes, but is not limited to, inflammation that is one or more of the following: acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing, seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative. Inflammatory disorders further include, without being limited to those affecting the blood vessels (polyarteritis, temporal arthritis); joints (arthritis: crystalline, osteo-, psoriatic, reactive, rheumatoid, Reiter's); gastrointestinal tract (Disease,); skin (dermatitis); or multiple organs and tissues (systemic lupus erythematosus).

[00087] The term "modulate," as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[00088] The term "modulator," as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an agonist or an antagonist.

[00089] The terms "ocular disease" or "ophthalmic disease," as used herein, refer to diseases which affect the eye or eyes and potentially the surrounding tissues as well. Ocular or ophthalmic diseases include, but are not limited to, conjunctivitis, retinitis, scleritis, uveitis, allergic conjuctivitis, vernal conjunctivitis, papillary conjunctivitis and cytomegalovirus (CMV) retinitis.

[00090] The term "pharmaceutically acceptable," as used herein, refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compounds described herein. Such materials are administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the

composition in which it is contained.

[00091] The term "pharmaceutically acceptable salt," as used herein, refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compounds described herein.

[00092] The terms "combination" or "pharmaceutical combination," as used herein mean a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, by way of example, a compound of Formula (I) and an additional therapeutic agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, by way of example, a compound of Formula (I) and an additional therapeutic agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

[00093] The terms "composition" or "pharmaceutical composition," as used herein, refers to a mixture of at least one compound, such as the compounds of Formula (I) described herein, with at least one and optionally more than one other pharmaceutically acceptable chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients.

[00094] The term "prodrug," as used herein, refers to an agent that is converted into the parent drug *in vivo*. A non-limiting example of a prodrug of the compounds described herein is a compound described herein administered as an ester which is then metabolically hydrolyzed to a carboxylic acid, the active entity, once inside the cell. A further example of a prodrug is a short peptide bonded to an acid group where the peptide is metabolized to reveal the active moiety.

[00095] The term "respiratory disease," as used herein, refers to diseases affecting the organs that are involved in breathing, such as the nose, throat, larynx, trachea, bronchi, and lungs. Respiratory diseases include, but are not limited to, asthma, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, seasonal allergic rhinitis, perennial allergic rhinitis, chronic obstructive pulmonary disease, including

chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis, and hypoxia.

[00096] The term "subject" or "patient," as used herein, encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, humans, chimpanzees, apes monkeys, cattle, horses, sheep, goats, swine; rabbits, dogs, cats, rats, mice, guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like. Frequently the subject is a human, and may be a human who has been diagnosed as in need of treatment for a disease or disorder disclosed herein.

[00097] The term "TLR modulator," as used herein, refers to a compound which modulates a TLR receptor.

[00098] The term "TLR disease" or a "disease or disorder associated with TLR activity," as used herein, refers to any disease state associated with a toll-like receptor. Such diseases or disorders include, but are not limited to, infectious diseases, inflammatory diseases, respiratory diseases and autoimmune diseases, such as, by way of example only, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDs), Crohns disease, bronchitis, dermatitis, allergic rhinitis, psoriasis, scleroderma, urticaria, rheumatoid arthritis, multiple sclerosis, cancer, HIV and lupus.

[00099] The term "therapeutically effective amount," as used herein, refers to any amount of a compound which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

[000100] The terms "treat," "treating" or "treatment," as used herein, refers to methods of alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

[000101] Other objects, features and advantages of the methods, compositions and combinations described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only.

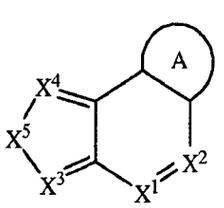
Description of the Preferred Embodiments

[000102] Provided herein are compounds and pharmaceutical compositions thereof, which are modulators of toll-like receptors (TLRs). In certain embodiments, certain compounds described herein, and pharmaceutical compositions thereof, are agonists of toll-like receptors. In other embodiments, such compounds and pharmaceutical compositions thereof, are agonists of TLR7. In other embodiments, such compounds and pharmaceutical compositions thereof, are agonists of TLR8. In other embodiments, such compounds and pharmaceutical compositions thereof, are agonists of both TLR7 and TLR8, that is such compounds and pharmaceutical compositions thereof, are dual agonists of TLR7 and TLR8.

[000103] Provided herein are compounds, pharmaceutical compositions and methods for the treatment and/or prevention of diseases and/or disorders associated with TLR activity. In certain embodiments, such TLRs are TLR7 and TLR8.

[000104] The TLR modulators provided herein include compounds having the structure of Formula (I), and pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof:

[000105] Provided herein are compounds, pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, having the structure of Formula (I):



Formula (I)

wherein:

X^1 is N or $CN(R^1R^2)$; X^2 is N or $CN(R^1R^2)$, provided that when X^1 is $CN(R^1R^2)$ then X^2 is N;

X^3 is N or CR^6;

X^4 is N or CR^3; and X^5 is $-CR^4=CR^5-$, $-CR^4=N-$ or $-N=CR^5-$;

R^1 and R^2 are each independently selected from H, $-C(O)R^8$, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl,

wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_3-C_8cycloalkyl, or C_3-C_8heterocycloalkyl groups of R^1 and R^2 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, =O, C_1-C_6 alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_3-C_8cycloalkyl, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-C(O)N(R^9)_2$, C_3-C_8heterocycloalkyl, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, $-N R^9S(O)_2R^8$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$, $-OLP(O)(OR^{10})_2$, C_1-C_6haloalkyl and C_1-C_6haloalkoxy, and

wherein the aryl and heteroaryl groups of R^1 and R^2 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, C_1-C_6 alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_3-C_8cycloalkyl, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-C(O)N(R^9)_2$, C_3-C_8heterocycloalkyl, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, $-NR^9S(O)_2R^8$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$, $-OLP(O)(OR^{10})_2$, C_1-C_6haloalkyl and C_1-C_6haloalkoxy,

or R^1 and R^2 are each independently C_1-C_6alkyl that can be substituted as described above and, taken together with the N atom to which they are attached, form an optionally substituted C_3-C_8heterocycloalkyl;

R^3 and R^6 are each independently selected from H, halogen, C_1-C_6alkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl,

wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, or C_3-C_8heterocycloalkyl groups of R^3 and R^6 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, =O, R^7, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-C(O)N(R^9)_2$, $-S(O)_2R^8$, $-S(O)_2 N(R^9)_2$ and $-NR^9S(O)_2R^8$, and

wherein the aryl and heteroaryl groups of R^3 and R^6 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, R^7, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-C(O)N(R^9)_2$, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$ and $-NR^9S(O)_2R^8$;

R^4 and R^5 are each independently selected from H, halogen, -C(O)OR^7, -C(O)R^7, -C(O)N($R^{11}R^{12}$), -N($R^{11}R^{12}$), -N(R^9)$_2$, -NHN(R^9)$_2$, -SR^7, -$(CH_2)_n$OR^7, -$(CH_2)_n$$R^7$, -L$R^8$, -L$R^{10}$, -OL$R^8$, -OL$R^{10}$, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl,

wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, or C_3-C_8heterocycloalkyl groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, =O, -NO_2, -R^7, -OR^8, -C(O)R^8, -OC(O)R^8, -C(O)OR^8, -N(R^9)$_2$, -P(O)(OR^8)$_2$, -OP(O)(OR^8)$_2$, -P(O)(OR^{10})$_2$, -OP(O)(OR^{10})$_2$, -C(O)N(R^9)$_2$, -Si(R^8)$_3$, –S(O)$_2$$R^8$, –S(O)$R^8$, –S(O)$_2$N($R^9$)$_2$, and -N$R^9$S(O)$_2$$R^8$, and

wherein the aryl and heteroaryl groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, -R^7, -OR^8, -C(O)R^8, -OC(O)R^8, -C(O)OR^8, -N(R^9)$_2$, -P(O)(OR^8)$_2$, -OP(O)(OR^8)$_2$, -P(O)(OR^{10})$_2$, -OP(O)(OR^{10})$_2$, -C(O)N(R^9)$_2$, -Si(R^8)$_3$, –S(O)$_2$$R^8$, –S(O)$R^8$, –S(O)$_2$N($R^9$)$_2$, and -N$R^9$S(O)$_2$$R^8$;

or R^3 and R^4, or R^4 and R^5, or R^5 and R^6, when present on adjacent ring atoms, can optionally be linked together to form a 5-6 membered ring, wherein the 5-6 membered ring is optionally substituted with R^7;

each L is independently selected from a bond, -$(O(CH_2)_m)_t$-, C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene, wherein the C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene of L are each optionally substituted with 1 to 4 substituents independently selected from halogen, -R^8, -OR^8, -N(R^9)$_2$, -P(O)(OR^8)$_2$, -OP(O)(OR^8)$_2$, -P(O)(OR^{10})$_2$, and -OP(O)(OR^{10})$_2$;

R^7 is selected from H, C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, and C_3-C_8heterocycloalkyl,

wherein the C_1-C_6alkyl, C_3-C_8cycloalkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, or C_3-C_8heterocycloalkyl groups of R^7 are each optionally substituted with 1 to 3 R^{13} groups, and each R^{13} is independently selected from halogen, –CN,

=O, -LR^9, -LOR^9, -OLR^9, -LR^{10}, -LOR^{10}, -OLR^{10}, -LR^8, -LOR^8, -OLR^8, -LSR^8, -LSR^{10}, -LC(O)R^8, -OLC(O)R^8, -LC(O)OR^8, -LC(O)R^{10}, -LOC(O)OR^8, -LC(O)NR^{9}R^{11}, -LC(O)NR^{9}R^8, -LN(R^9)$_2$, -LNR^{9}R^8, -LNR^{9}R^{10}, -LC(O)N(R^9)$_2$, –LS(O)$_2$R^8, –LS(O)R^8, -LC(O)NR^{8}OH, -LNR^{9}C(O)R^8, -LNR^{9}C(O)OR^8, -LC(=N-OR^8)R^8, -LC(=NH)-NHOR^8, -NHC(=NH)NH$_2$, –LS(O)$_2$N(R^9)$_2$, -OLS(O)$_2$N(R^9)$_2$, -LNR^{9}S(O)$_2$R^8, -LC(O)NR^{9}LN(R^9)$_2$, -LP(O)(OR^8)$_2$, -LOP(O)(OR^8)$_2$, -LP(O)(OR^{10})$_2$ and -OLP(O)(OR^{10})$_2$;

wherein the aryl and heteroaryl groups of R^7 are each optionally substituted with 1 to 3 R^{13} groups, and each R^{13} is independently selected from halogen, –CN, -LR^9, -LOR^9, -OLR^9, -LR^{10}, -LOR^{10}, -OLR^{10}, -LR^8, -LOR^8, -OLR^8, -LSR^8, -LSR^{10}, -LC(O)R^8, -OLC(O)R^8, -LC(O)OR^8, -LC(O)R^{10}, -LOC(O)OR^8, -LC(O)NR^{9}R^{11}, -LC(O)NR^{9}R^8, -LN(R^9)$_2$, -LNR^{9}R^8, -LNR^{9}R^{10}, -LC(O)N(R^9)$_2$, -LS(O)$_2$R^8, –LS(O)R^8, -LC(O)NR^{8}OH, -LNR^{9}C(O)R^8, -LNR^{9}C(O)OR^8, -LC(=N-OR^8)R^8, -LC(=NH)-NHOR^8, -NHC(=NH)NH$_2$, –LS(O)$_2$N(R^9)$_2$, -OLS(O)$_2$N(R^9)$_2$, -LNR^{9}S(O)$_2$R^8, -LC(O)NR^{9}LN(R^9)$_2$, -LP(O)(OR^8)$_2$, -LOP(O)(OR^8)$_2$, -LP(O)(OR^{10})$_2$ and -OLP(O)(OR^{10})$_2$;

each R^8 is independently selected from H, -CH(R^{10})$_2$, C$_1$-C$_8$alkyl, C$_2$-C$_8$alkene, C$_2$-C$_8$alkyne, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$alkoxy, C$_1$-C$_6$heteroalkyl, C$_3$-C$_8$cycloalkyl, C$_2$-C$_8$heterocycloalkyl, C$_1$-C$_6$hydroxyalkyl and C$_1$-C$_6$haloalkoxy, wherein the C$_1$-C$_8$alkyl, C$_2$-C$_8$alkene, C$_2$-C$_8$alkyne, C$_1$-C$_6$heteroalkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$alkoxy, C$_3$-C$_8$cycloalkyl, C$_2$-C$_8$heterocycloalkyl, C$_1$-C$_6$hydroxyalkyl and C$_1$-C$_6$haloalkoxy groups of R^8 are each optionally substituted with 1 to 3 substituents independently selected from –CN, R^{11}, -OR^{11}, -SR^{11}, -C(O)R^{11}, -OC(O)R^{11}, -C(O)N(R^9)$_2$, -C(O)OR^{11}, -NR^{9}C(O)R^{11}, -NR^{9}R^{10}, -NR^{11}R^{12}, -N(R^9)$_2$, -OR^9, -OR^{10}, -C(O)NR^{11}R^{12}, -C(O)NR^{11}OH, –S(O)$_2$R^{11}, –S(O)R^{11}, –S(O)$_2$NR^{11}R^{12}, -NR^{11}S(O)$_2$R^{11}, -P(O)(OR^{11})$_2$, and -OP(O)(OR^{11})$_2$;

each R^9 is independently selected from H, -C(O)R^8, -C(O)OR^8, -C(O)R^{10}, -C(O)OR^{10}, -Si(R^8)$_3$, -S(O)$_2$R^{10}, -C$_1$-C$_6$ alkyl, C$_1$-C$_6$ heteroalkyl and C$_3$-C$_6$ cycloalkyl, or each R^9 is independently a C$_1$-C$_6$alkyl that together with N they are attached to form a C$_3$-C$_8$heterocycloalkyl, wherein the C$_3$-C$_8$heterocycloalkyl ring optionally

contains an additional heteroatom selected from N, O and S, and wherein the C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, or C_3-C_8heterocycloalkyl groups of R^9 are each optionally substituted with 1 to 3 substituents independently selected from –CN, R^{11}, -OR^{11}, -SR^{11}, -$C(O)R^{11}$, -$OC(O)R^{11}$, -$C(O)OR^{11}$, -$NR^{11}R^{12}$, -$C(O)NR^{11}R^{12}$, -$C(O)NR^{11}OH$, -$S(O)_2R^{11}$, -$S(O)R^{11}$, -$S(O)_2NR^{11}R^{12}$, -$NR^{11}S(O)_2R^{11}$, -$P(O)(OR^{11})_2$, and -$OP(O)(OR^{11})_2$;

each R^{10} is independently selected from aryl, C_3-C_8cycloalkyl, C_3-C_8heterocycloalkyl and heteroaryl, wherein the aryl, C_3-C_8cycloalkyl, C_3-C_8heterocycloalkyl and heteroaryl groups are optionally substituted with 1 to 3 substituents selected from halogen, –R^8, -OR^8, –LR^9, -LOR^9, -$N(R^9)_2$, -$NR^9C(O)R^8$, -$NR^9CO_2R^8$, -CO_2R^8, -$C(O)R^8$ and -$C(O)N(R^9)_2$;

R^{11} and R^{12} are independently selected from H, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl,

wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl groups of R^{11} and R^{12} are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, =O, R^8, –OR^8, -$C(O)R^8$, -$OC(O)R^8$, -$C(O)OR^8$, -$N(R^9)_2$, -$NR^8C(O)R^8$, -$NR^8C(O)OR^8$, -$C(O)N(R^9)_2$, C_3-C_8heterocycloalkyl, –$S(O)_2R^8$, –$S(O)_2N(R^9)_2$, -$NR^9S(O)_2R^8$, C_1-C_6haloalkyl and C_1-C_6haloalkoxy, and

wherein the aryl and heteroaryl groups of R^{11} and R^{12} are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, R^8, –OR^8, -$C(O)R^8$, -$OC(O)R^8$, -$C(O)OR^8$, -$N(R^9)_2$, -$NR^8C(O)R^8$, -$NR^8C(O)OR^8$, -$C(O)N(R^9)_2$, C_3-C_8heterocycloalkyl, –$S(O)_2R^8$, –$S(O)_2N(R^9)_2$, -$NR^9S(O)_2R^8$, C_1-C_6haloalkyl and C_1-C_6haloalkoxy,

or R^{11} and R^{12} are each independently C_1-C_6alkyl and taken together with the N atom to which they are attached form an optionally substituted C_3-C_8heterocycloalkyl ring optionally containing an additional heteroatom selected from N, O and S;

Ring A is an aryl or a heteroaryl, wherein the aryl or heteroaryl groups of Ring A are optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from halogen, –R^8, –R^7, -OR^7, -OR^8, –R^{10}, -OR^{10}, -SR^8, -NO_2, -CN, -

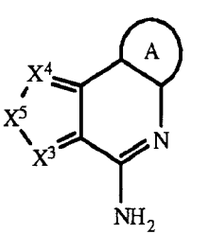
$N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$, and two adjacent substituents on Ring A can be joined to form a 5-6 membered ring that can contain up to two heteroatoms as ring members;

n is, independently at each occurrence, 0, 1, 2, 3, 4, 5, 6, 7 or 8;

each m is independently selected from 1, 2, 3, 4, 5 and 6, and

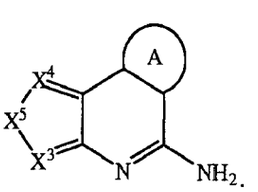
t is 1, 2, 3, 4, 5, 6, 7 or 8.

[000106] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (I-A),



Formula (I-A).

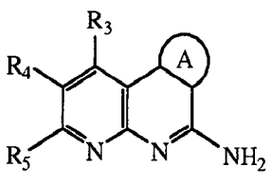
[000107] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (I-B),



Formula (I-B).

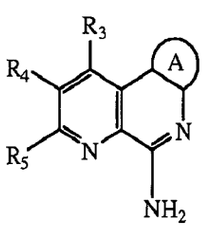
[000108] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of

Formula (II),



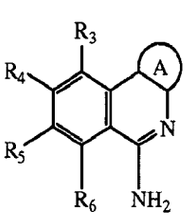
Formula (II).

[000109] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (III),



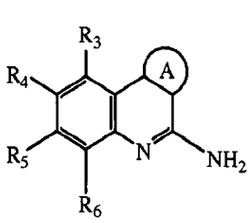
Formula (III).

[000110] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (IV),



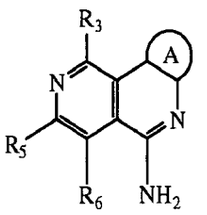
Formula (IV).

[000111] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (V),



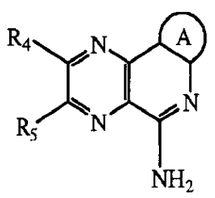
Formula (V).

[000112] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (VI),



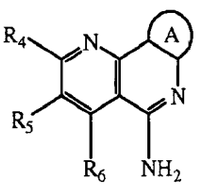
Formula (VI).

[000113] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (VII),



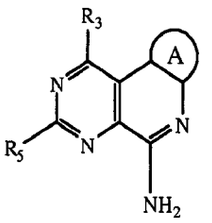
Formula (VII).

[000114] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (VIII),



Formula (VIII).

[000115] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (IX),



Formula (IX).

[000116] In certain embodiments of compounds of Formulas (I)-(IX), Formula (I-A) and Formula (I-B), ring A is selected from phenyl, naphthyl, fluorenyl, indenyl, azulenyl and anthracenyl, each of which is optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$. In other embodiments of compounds of Formulas (I)-(IX), Formula (I-A) and Formula (I-B), Ring A is phenyl or naphthyl, each of which is optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$.

[000117] In certain embodiments of compounds of Formulas (I)-(IX), Formula (I-A) and Formula (I-B), ring A is selected from benzofuranyl, benzofurazanyl, benzoxazolyl, benzopyranyl, benzthiazolyl, benzothienyl, benzazepinyl, benzimidazolyl, benzothiopyranyl, benzo[1,3]dioxole, benzo[b]furyl, benzo[b]thienyl, cinnolinyl, furazanyl, furyl, furopyridinyl, imidazolyl, indolyl, indolizinyl, indolin-2-one, indazolyl, isoindolyl, isoquinolinyl, isoxazolyl, isothiazolyl, 1,8-naphthyridinyl, oxazolyl, oxaindolyl, oxadiazolyl, pyrazolyl, pyrrolyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinoxalinyl, quinolinyl, quinazolinyl, 4H-quinolizinyl, thiazolyl, thiadiazolyl, thienyl, triazinyl,triazolyl and

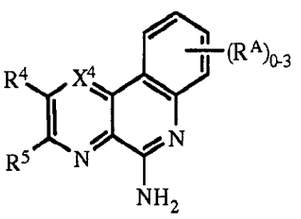
tetrazolyl, each of which is optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$. In other embodiments of compounds of Formulas (I)-(IX), Formula (I-A) and Formula (I-B), Ring A is selected from pyridyl, benzo[1,3]dioxole, thienyl, benzothienyl, benzofuranyl, or indolyl, each of which is optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$.

[000118] In certain embodiments of compounds of Formulas (I)-(IX), Formula (I-A) and Formula (I-B), Ring A is selected from phenyl, thienyl, and pyridyl, and in other embodiments such phenyl, thienyl, and pyridyl groups are optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$.

[000119] In certain embodiments of compounds of Formulas (I)-(IX), Formula (I-A) and Formula (I-B), Ring A is a phenyl optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$,

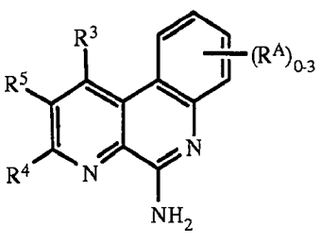
$-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$. In certain embodiments of compounds of Formulas (I)-(IX), Formula (I-A) and Formula (I-B), Ring A is a pyridyl optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$.

[000120] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (X),



Formula (X).

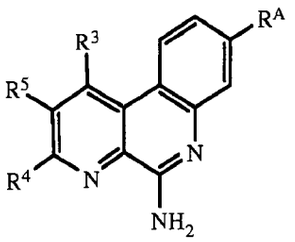
[000121] In certain embodiments compounds of Formula (X), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (X-A),



Formula (X-A).

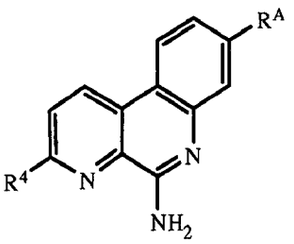
[000122] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives,

protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (XI),

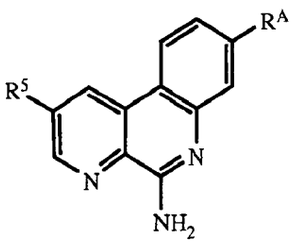


Formula (XI).

[000123] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (XII) or Formula (XIII),



Formula (XII)



Formula (XIII).

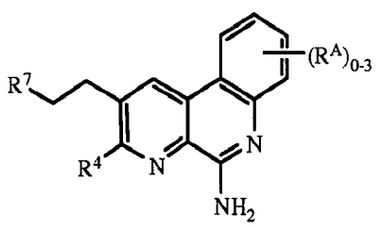
[000124] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIII), R^4 and R^5, when present, are independently selected from H, halogen, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-SR^7$, $-(CH_2)_nOR^7$, $-(CH_2)_nR^7$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, or C_3-C_8heterocycloalkyl groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, $-CN$, $=O$, $-NO_2$, $-R^7$, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-C(O)N(R^9)_2$, $-Si(R^8)_3$, $-S(O)_2R^8$, $-S(O)R^8$, $-S(O)_2N(R^9)_2$, and $-NR^9S(O)_2R^8$, and wherein the aryl and heteroaryl groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, $-CN$, $-R^7$, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-C(O)N(R^9)_2$, $-Si(R^8)_3$, $-S(O)_2R^8$, $-S(O)R^8$, $-S(O)_2N(R^9)_2$, and $-NR^9S(O)_2R^8$. In other embodiments, R^3 and R^4,

or R^4 and R^5, or R^5 and R^6, when present on adjacent ring atoms, can optionally be linked together to form a 5-6 membered ring, wherein the 5-6 membered ring is optionally substituted with R^7.

[000125] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIII), each L is independently selected from a bond, $-(O(CH_2)_m)_t-$, C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene, wherein the C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene of L are each optionally substituted with 1 to 4 substituents independently selected from halogen, $-R^8$, $-OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, and $-OP(O)(OR^{10})_2$.

[000126] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIII), R^4 and R^5, when present, are independently selected from H, halogen, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-SR^7$, $-(CH_2)_nOR^7$, $-(CH_2)_nR^7$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_3-C_8heterocycloalkyl, aryl and heteroaryl groups of R^4 and R^5 are each optionally substituted with 1 to 3 R^7.

[000127] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (XIV),



Formula (XIV).

[000128] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIV), R^7 is selected from H, C_1-C_6alkyl, C_3-C_8cycloalkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_8cycloalkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, and C_3-C_8heterocycloalkyl groups of R^7 are each optionally substituted with 1 to 3 R^{13} groups and each R^{13} is independently selected from halogen –CN, =O, $-LR^9$, $-LOR^9$, $-OLR^9$, $-LR^{10}$, $-LOR^{10}$, $-OLR^{10}$, $-LR^8$, $-LOR^8$, $-OLR^8$, $-LSR^8$, $-LSR^{10}$, $-LC(O)R^8$, $-OLC(O)R^8$, $-LC(O)OR^8$, $-LC(O)R^{10}$, $-LOC(O)OR^8$, $-LC(O)NR^9R^{11}$, $-LC(O)NR^9R^8$, $-LN(R^9)_2$, $-LNR^9R^8$, $-LNR^9R^{10}$, -

$LC(O)N(R^9)_2$, $-LS(O)_2R^8$, $-LS(O)R^8$, $-LC(O)NR^8OH$, $-LNR^9C(O)R^8$, $-LNR^9C(O)OR^8$, $-LC(=N-OR^8)R^8$, $-LC(=NH)-NHOR^8$, $-NHC(=NH)NH_2$, $-LS(O)_2N(R^9)_2$, $-OLS(O)_2N(R^9)_2$, $-LNR^9S(O)_2R^8$, $-LC(O)NR^9LN(R^9)_2$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$ and $-OLP(O)(OR^{10})_2$.

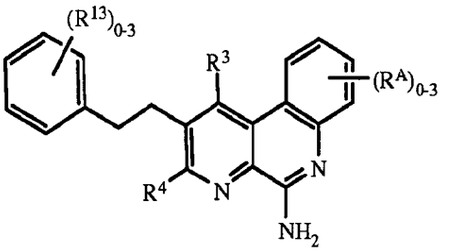
[000129] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIV), R^7 is an aryl or heteroaryl group optionally substituted with 1 to 3 R^{13} groups and each R^{13} is independently selected from halogen, $-CN$, $-LR^9$, $-LOR^9$, $-OLR^9$, $-LR^{10}$, $-LOR^{10}$, $-OLR^{10}$, $-LR^8$, $-LOR^8$, $-OLR^8$, $-LSR^8$, $-LSR^{10}$, $-LC(O)R^8$, $-OLC(O)R^8$, $-LC(O)OR^8$, $-LC(O)R^{10}$, $-LOC(O)OR^8$, $-LC(O)NR^9R^{11}$, $-LC(O)NR^9R^8$, $-LN(R^9)_2$, $-LNR^9R^8$, $-LNR^9R^{10}$, $-LC(O)N(R^9)_2$, $-LS(O)_2R^8$, $-LS(O)R^8$, $-LC(O)NR^8OH$, $-LNR^9C(O)R^8$, $-LNR^9C(O)OR^8$, $-LC(=N-OR^8)R^8$, $-LC(=NH)-NHOR^8$, $-NHC(=NH)NH_2$, $-LS(O)_2N(R^9)_2$, $-OLS(O)_2N(R^9)_2$, $-LNR^9S(O)_2R^8$, $-LC(O)NR^9LN(R^9)_2$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$ and $-OLP(O)(OR^{10})_2$.

[000130] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIV), R^7 is selected from H, C_1-C_6alkyl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, and the C_1-C_6alkyl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl groups are each optionally substituted with 1-3 R^{13} groups and each R^{13} is independently selected from halogen, =O, C_1-C_6haloalkyl, LR^8, LR^9, OLR^8 and $-LOR^8$.

[000131] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIV), R^7 is an aryl or heteroaryl group optionally substituted with 1-3 R^{13} groups and each R^{13} is independently selected from halogen, C_1-C_6haloalkyl, LR^8, LR^9, OLR^8 and $-LOR^8$.

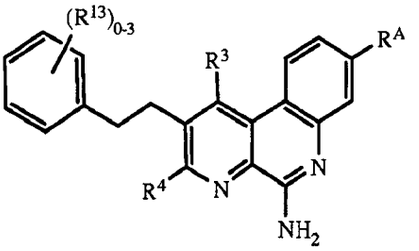
[000132] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIV), each L is independently selected from a bond, $-(O(CH_2)_m)_t-$, C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene, wherein the C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene of L are each optionally substituted with 1 to 4 substituents independently selected from halogen, $-R^8$, $-OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, and $-OP(O)(OR^{10})_2$.

[000133] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (XV),



Formula (XV).

[000134] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (XVI),



Formula (XVI).

[000135] In certain compounds of Formula (XV) or (XVI), R^4, R^A and R^{13} are independently selected from H, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH_2OH$, $-OCH_3$, $-COOCH_3$, $-COOCH_2CH_3$, F, Cl, Br, $-CH_2OCH_3$, $CH_2OCH_2CH_3$, $-N(CH_3)_2$, $-((O(CH_2)_2)_{2-4}OH$, $-O(CH_2)_{2-4}-OH$, $-O(CH_2)_{2-4}-(PO_3H_2)$, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}-CH(CH_3)_2$, C_2-C_6 alkyl substituted with 1-3 substituents selected from –OH, $-CH_3$, cyclopropyl, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}(PO_3H_2)$, -COOH, $COOCH_3$, and $-COOCH_2CH_3$. In some embodiments of such compounds, R^4 is H. In certain of these compounds, the phenyl ring of the phenethyl group has one to three R^{13} groups. Optionally, R^A is H or $-CH_3$. In certain embodiments, these compounds have two R^{13} groups present, and those R^{13} groups are selected from the group consisting of of $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH_2OH$, $-OCH_3$, $-COOCH_3$, $-COOCH_2CH_3$, F, Cl, Br, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-N(CH_3)_2$, $-((O(CH_2)_2)_{2-4}OH$, $-O(CH_2)_{2-4}-OH$, $-O(CH_2)_{2-4}-(PO_3H_2)$, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}-CH(CH_3)_2$, C_2-C_6 alkyl substituted with 1-3 substituents selected from –OH, $-CH_3$, cyclopropyl, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}(PO_3H_2)$, -COOH, $COOCH_3$, and $-COOCH_2CH_3$.

[000136] In certain embodiments of the compounds of Formula XIII, XIV, XV or XVI, the

compound is selected from: 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 2-(4-(dimethylamino)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine, and 2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine. Each of these compounds individually comprises a preferred embodiment of the compounds, compositions, and methods described herein.

[000137] In certain embodiments compounds of Formula (I) as described herein are combined with an antigen, and optionally a carrier, pharmaceutically acceptable excipient or adjuvant, to provide an immunogenic composition. In certain embodiments compounds of Formula (XVI) as described herein are combined with an antigen, and optionally a carrier, pharmaceutically acceptable excipient or adjuvant, to provide an immunogenic composition. In other embodiments, such immunogenic composition comprise a compound of Formula (I) and an antigen, wherein the antigen includes, but is not limited to, a bacterial antigen, a viral antigen, a fungal antigen, a tumor antigen, or an antigen associated with an STD, Alzheimer's, respiratory disorders, autoimmune disorders such as, by way of example only, rheumatoid arthritis or lupus, pediatric disorders and obesity, and wherein the amount of the compound is an amount effective to enhance an immune response to the antigen in a subject to whom the composition is administered. In other embodiments, such immunogenic composition comprise a compound of Formula (XVI) and an antigen, wherein the antigen includes, but is not limited to, a bacterial antigen, a viral antigen, a fungal antigen, a tumor antigen, or an antigen associated with an STD, Alzheimer's, respiratory disorders, autoimmune disorders such as, by way of example only, rheumatoid arthritis or lupus, pediatric disorders and obesity, and wherein the amount of the compound is an amount effective to enhance an immune response to the antigen in a subject to whom the composition is administered. Suitable antigens for use in such immunogenic compositions are described herein.

[000138] In certain embodiments, such immunogenic compositions include a bacterial antigen of a strain of *Neisseria meningitides*, such as serogroup A, C, W135, Y and/or B. Specific antigens for use in these compositions are described herein. In other embodiments, such immunogenic compositions, and others provided herein, are used as vaccines; their use in the treatment of disorders associated with the antigen included in the composition is described herein.

[000139] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XVI), each R^{13} is independently selected from LR^{10}, LOR^{10}, LR^8, $-LOR^8$, $-LSR^8$, LSR^{10}, $-LC(O)OR^8$, $-LN(R^9)_2$, $-LC(O)N(R^9)_2$, $-LS(O)_2R^8$, $-LS(O)R^8$, $-LP(O)(OR^8)_2$, $-OLP(O)(OR^8)_2$, $-LP(O)(O\,R^{10})_2$ and $-OLP(O)(OR^{10})_2$.

[000140] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XVI), each L is independently selected from a bond, $-(O(CH_2)_m)_t-$, C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene, wherein the C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene of L are each optionally substituted with 1 to 4 substituents independently selected from halogen, $-R^8$, $-OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, and $-OP(O)(OR^{10})_2$.

[000141] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XVI), R^1 and R^2 are each H.

[000142] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XVI), R^3 and R^6, when present, are independently selected from H, halogen, C_1-C_6alkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy.

[000143] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XVI), R^{10} is an aryl or a heteroaryl, wherein the aryl and heteroaryl groups are optionally substituted with 1 to 3 substituents selected from halogen, $-R^8$, $-OR^8$, LR^9 and $-N(R^9)_2$. In other embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XVI), R^{10} is phenyl optionally substituted with 1 to 3 substituents selected from halogen, $-R^8$, $-OR^8$, and $-N(R^9)_2$.

[000144] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIII), R^8 is selected from H, C_1-C_6alkyl and C_1-C_6haloalkyl.

[000145] In certain embodiments the compound of Formulas (I) is 3-chloro-2-methylbenzo[f][1,7]naphthyridin-5-amine; 2-methylbenzo[f][1,7]naphthyridin-5-amine; pyrimido[4,5-c]quinolin-5-amine; 2-(ethoxymethyl)benzo[f][1,7]naphthyridin-5-amine; pyrimido[4,5-c]quinoline-3,5-diamine; 3-(methylthio)pyrimido[4,5-c]quinolin-5-amine; (E)-2-(2-cyclopropylvinyl)benzo[f][1,7]naphthyridin-5-amine; (E)-2-(pent-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 4-(5-aminobenzo[f][1,7]naphthyridin-2-yl)-2-methylbut-3-yn-2-ol; 2-pentylbenzo[f][1,7]naphthyridin-5-amine; (E)-2-(prop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; (E)-2-(3-phenylprop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-cyclopropylethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(5-aminobenzo[f][1,7]naphthyridin-2-yl)-2-methylbutan-2-ol; 2-propylbenzo[f][1,7]naphthyridin-5-amine; 2-(3-phenylpropyl)benzo[f][1,7]naphthyridin-5-amine; 2-ethylbenzo[f][1,7]naphthyridin-5-

amine; 2-(2-methylprop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 2-isobutylbenzo[f][1,7]naphthyridin-5-amine; (E)-2-(2,4-difluorostyryl)benzo[f][1,7]naphthyridin-5-amine; (E)-2-(hex-1-enyl)benzo[f][1,7]naphthyridin-5-amine; (E)-2-(2-cyclohexylvinyl)benzo[f][1,7]naphthyridin-5-amine; E)-2-(3-(trifluoromethyl)styryl)benzo[f][1,7]naphthyridin-5-amine; (E)-2-(3-methoxystyryl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-vinylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-methyl-2-styrylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-cyclohexylethyl)benzo[f][1,7]naphthyridin-5-amine; 2-fluorobenzo[f][1,7]naphthyridin-5-amine; 2-(3-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-difluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-hexylbenzo[f][1,7]naphthyridin-5-amine; 2-ethyl-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; methyl 5-aminobenzo[f][1,7]naphthyridine-3-carboxylate; 5-amino-N-methylbenzo[f][1,7]naphthyridine-3-carboxamide; (5-aminobenzo[f][1,7]naphthyridin-3-yl)methanol; 8-phenylbenzo[f][1,7]naphthyridin-5-amine; 3-(ethoxymethyl)benzo[f][1,7]naphthyridin-5-amine; benzo[f][1,7]naphthyridine-3,5-diamine; benzo[f][1,7]naphthyridin-5-amine; methyl 5-aminobenzo[f][1,7]naphthyridine-8-carboxylate; 5-aminobenzo[f][1,7]naphthyridine-8-carboxylic acid; ethyl 5-aminobenzo[f][1,7]naphthyridine-8-carboxylate; (5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol; 5-aminobenzo[f][1,7]naphthyridine-3-carboxylic acid; 5-aminobenzo[f][1,7]naphthyridine-3-carbaldehyde; 2-(o-tolylethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-(m-tolylethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-(p-tolylethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 3-chloro-2-(ethoxymethyl)benzo[f][1,7]naphthyridin-5-amine; pyrazino[2,3-c]quinolin-5-amine; 9-chlorobenzo[f][1,7]naphthyridin-5-amine; 8-chlorobenzo[f][1,7]naphthyridin-5-amine; 9-methylbenzo[f][1,7]naphthyridin-5-amine; 10-methylbenzo[f][1,7]naphthyridin-5-amine; ethyl 5-aminobenzo[f][1,7]naphthyridine-9-carboxylate; 5-aminobenzo[f][1,7]naphthyridine-9-carboxylic acid; 8-methoxybenzo[f][1,7]naphthyridin-5-amine; 7-fluorobenzo[f][1,7]naphthyridin-5-amine; 8-(methylsulfonyl)benzo[f][1,7]naphthyridin-5-amine; 8-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine; 8-fluorobenzo[f][1,7]naphthyridin-5-amine;

3-methoxybenzo[f][1,7]naphthyridin-5-amine; 3-butoxybenzo[f][1,7]naphthyridin-5-amine; 3-(benzyloxy)benzo[f][1,7]naphthyridin-5-amine; 3-methylbenzo[f][1,7]naphthyridin-5-amine; 3-chlorobenzo[f][1,7]naphthyridin-5-amine; N^3,N^3-dimethylbenzo[f][1,7]naphthyridine-3,5-diamine; N^3-butylbenzo[f][1,7]naphthyridine-3,5-diamine; 3-vinylbenzo[f][1,7]naphthyridin-5-amine; 3-ethylbenzo[f][1,7]naphthyridin-5-amine; 3-fluorobenzo[f][1,7]naphthyridin-5-amine; 2-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine; 2-methoxybenzo[f][1,7]naphthyridin-5-amine; 2-(benzyloxy)benzo[f][1,7]naphthyridin-5-amine; 2-vinylbenzo[f][1,7]naphthyridin-5-amine; 2-phenylbenzo[f][1,7]naphthyridin-5-amine; (E)-2-styrylbenzo[f][1,7]naphthyridin-5-amine; 2-phenethylbenzo[f][1,7]naphthyridin-5-amine; (E)-2-(3-methoxyprop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-methoxypropyl)benzo[f][1,7]naphthyridin-5-amine; 2-(prop-1-en-2-yl)benzo[f][1,7]naphthyridin-5-amine; 2-isopropylbenzo[f][1,7]naphthyridin-5-amine; 1-methylbenzo[f][1,7]naphthyridin-5-amine; benzo[c][1,8]naphthyridin-6-amine; pyrido[3,2-f][1,7]naphthyridin-6-amine; thieno[2,3-c]quinolin-4-amine; 8-methyl-2-(naphthalen-2-ylethynyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(naphthalen-1-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(naphthalen-2-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(naphthalen-1-ylethynyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoic acid; 3-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoic acid; 2-(3-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (3-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol; 2-(4-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-(trifluoromethyl)phenanthridin-6-amine; benzo[c][2,7]naphthyridin-5-amine; 2-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine; 2-tert-butoxybenzo[f][1,7]naphthyridin-5-amine; 5-aminobenzo[f][1,7]naphthyridin-2-ol; 2-((4-butylphenyl)ethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-butylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-benzyl-5-chloro-7-(trifluoromethyl)-1,2-dihydropyrido[3,4-b]pyrazin-3(4H)-one; 2-(2-(6-methoxynaphthalen-2-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-butylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-propylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,5-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-propylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2,4,5-

trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,5-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-isopropylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-heptylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (Z)-2-(2-(biphenyl-4-yl)vinyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-isobutoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-((2-methoxyethoxy)methoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-phenoxyethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(tert-butyldimethylsilyloxy)ethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-butoxy-2-methylphenethyl)-N-butyl-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-phenylbutoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(allyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(3-phenylpropoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(heptan-4-yloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-methylpent-3-enyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-cyclohexylethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-isopropoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(3,3-dimethylbutoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(tert-butyldimethylsilyloxy)ethoxy)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; diethyl 3-(2-(4-(2-(2-hydroxyethoxy)ethoxy)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-ylamino)propylphosphonate; (E)-N-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)vinyl)phenyl)acetamide; N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide; N-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide; N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-4-methylbenzenesulfonamide; 3-methyl-9-p-tolyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzonitrile; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-aminoethyl)-3-methylbenzamide; 2-(4-(2-(5-amino-3-chloro-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetic acid; (S)-2-(4-(2-(5-amino-3-chloro-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoic acid; 4-(2-

(5-amino-3-chloro-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide; 8-methyl-2-(2-methyl-4-(1H-tetrazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; methyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoate; methyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetic acid; 6-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)hexan-1-ol; 7-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)heptanoic acid; 11-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)undecan-1-ol; 2-phenethylbenzo[f][1,7]naphthyridin-5-amine; ethyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)acetate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)acetic acid; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propanoic acid; 6-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)hexanoic acid; 8-methyl-2-(2-methyl-4-(methylthio)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(methylsulfonyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(hexyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-phenethoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-cyclobutoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(pentyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-methylpentyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-bromo-3-methoxybenzo[f][1,7]naphthyridin-5-amine; 2-((tert-butyldimethylsilyl)ethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-((2-fluorophenyl)ethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-((3-fluorophenyl)ethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-((4-fluorophenyl)ethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-(thiophen-3-ylethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-ethynylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(thiophen-3-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; ethyl 5-aminobenzo[f][1,7]naphthyridine-2-

carboxylate; ethyl 5-amino-8-methylbenzo[f][1,7]naphthyridine-2-carboxylate; (5-aminobenzo[f][1,7]naphthyridin-2-yl)methanol; 2-(3,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-chloro-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-1-(3-phenylpropyl)benzo[f][1,7]naphthyridin-5-amine; (Z)-2-(2-(benzo[d][1,3]dioxol-5-yl)vinyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (Z)-2-(4-methoxy-2-methylstyryl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(3,4-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(3,5-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(1-phenylvinyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-phenylbutyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(1-phenylethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(benzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (Z)-2-(2-ethoxyvinyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-ethoxyethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(chloromethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-nitroethyl)benzo[f][1,7]naphthyridin-5-amine; diethyl 2-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)methyl)malonate; 2-(isopropylsulfonyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-((methoxymethoxy)methyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-((methylamino)methyl)benzo[f][1,7]naphthyridin-5-amine; tert-butyl 5-amino-8-methylbenzo[f][1,7]naphthyridin-2-ylcarbamate; 8-methyl-2-((phenylamino)methyl)benzo[f][1,7]naphthyridin-5-amine; 2-(aminomethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(pyrrolidin-1-ylmethyl)benzo[f][1,7]naphthyridin-5-amine; N^2-(2,4-dimethoxybenzyl)-8-methylbenzo[f][1,7]naphthyridine-2,5-diamine; N^2,N^2,8-trimethylbenzo[f][1,7]naphthyridine-2,5-diamine; N^2,8-dimethylbenzo[f][1,7]naphthyridine-2,5-diamine; 8-methyl-2-(pyrrolidin-1-yl)benzo[f][1,7]naphthyridin-5-amine; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-phenylethanol; 2-(2-aminoethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-hydrazinyl-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-2-methylpropan-2-ol; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(4-methoxyphenyl)ethanol; 2-(biphenyl-2-yl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,6-dimethylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(5-methoxypyridin-2-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoic acid; 5-(2-(5-amino-8-

methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-4-methylpyridin-2(1H)-one; 6-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)pyridin-3-ol; 3-methyldibenzo[b,f][1,7]naphthyridin-6-amine; 8-methyl-2-(4-(trifluoromethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,3-dihydro-1H-inden-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,3-dihydro-1H-inden-5-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; (E)-3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylic acid; (E)-ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylate; N^3,N^5-dibutylbenzo[f][1,7]naphthyridine-3,5-diamine; 8-(prop-1-en-2-yl)benzo[f][1,7]naphthyridin-5-amine; 5-aminobenzo[f][1,7]naphthyridine-8-carbonitrile; (E)-8-(3-methylbut-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-methylprop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; (E)-8-(pent-1-enyl)benzo[f][1,7]naphthyridin-5-amine; (E)-8-styrylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-(2-cyclopropylvinyl)-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; 8-pentylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-(2-cyclopropylvinyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; pyrido[1,2-c][1,7]naphthyridin-6-amine; 9-phenethylpyrido[1,2-c][1,7]naphthyridin-6-amine; methyl 5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridine-8-carboxylate; 8-nitrobenzo[f][1,7]naphthyridin-5-amine; 3-chloro-8-methylbenzo[f][1,7]naphthyridin-5-amine; methyl 5-amino-3-chlorobenzo[f][1,7]naphthyridine-8-carboxylate; methyl 5-amino-3-fluorobenzo[f][1,7]naphthyridine-8-carboxylate; 3-chloro-8-nitrobenzo[f][1,7]naphthyridin-5-amine; (5-amino-3-chlorobenzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-phenethylbenzo[f][1,7]naphthyridin-8-yl)methanol; 4-(2-(5-amino-8-fluorobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzaldehyde; 2-(4-(2-(5-amino-8-fluorobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzylamino)ethanol; 3-(4-(2-(5-amino-8-fluorobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzylamino)propan-1-ol; 8-fluoro-2-(4-((2-methoxyethylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-((tert-butyldimethylsilyloxy)methyl)-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 3-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol; 2-(2-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-ethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-ethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-

(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(piperidin-1-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-tert-butylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(piperidin-1-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(3,5-dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(1-methyl-1H-imidazol-5-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-hydroxybenzimidamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzonitrile; 8-methyl-2-(4-(1-morpholinoethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-aminophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)guanidine; 8-methyl-2-(4-(1-(phenethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetonitrile; 2-(4-(piperidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzyl)piperidin-4-ol; 2-(4-(aminomethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-((ethylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-aminopropan-2-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-(1-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid; 8-methyl-2-(4-(1-(phenylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-ethyl-8-methylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)methanol; 8-methyl-2-propylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(1H-indol-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-ethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-phenoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol; 2-(2-(2,3-dihydrobenzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-

yl)ethanol; 3-methyl-9-phenyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine; 8-methylbenzo[f][1,7]naphthyridine-2,5-diamine; 1-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)propan-2-ol; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetonitrile; N-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetamide; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(2,4-dimethylphenyl)ethanol; 2-(2-(6-methoxy-4-methylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)butan-1-ol; methyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoate; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-1-ol; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-2-methylbutan-2-ol; 2-(4-(aminomethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (E)-ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylate; ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzyl)propane-1,3-diol; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoic acid; 5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridine-8-carbaldehyde; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoate; 8-methyl-2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-2-ol; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoic acid; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)methanol; 8-methyl-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 8-methyl-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; (E)-ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylate; (E)-3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylic acid; ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoate; 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoic acid; 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propan-1-ol; (5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol; 5-aminobenzo[f][1,7]naphthyridin-8-ol; 5-aminobenzo[f][1,7]naphthyridine-8-

carbaldehyde; 1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanol; 1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanone; 8-isopropylbenzo[f][1,7]naphthyridin-5-amine; 8-vinylbenzo[f][1,7]naphthyridin-5-amine; 8-ethylbenzo[f][1,7]naphthyridin-5-amine; 8-(methoxymethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-phenethylbenzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; benzo[f][1,7]naphthyridine-5,8-diamine; 8-(aminomethyl)benzo[f][1,7]naphthyridin-5-amine; 3-fluoro-8-methylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-3-fluorobenzo[f][1,7]naphthyridin-8-yl)methanol; 3-chlorobenzo[f][1,7]naphthyridine-5,8-diamine; 3-fluorobenzo[f][1,7]naphthyridine-5,8-diamine; 8-isobutylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-(prop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 8-propylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)benzo[f][1,7]naphthyridin-5-amine; 8-phenethylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(4-bromophenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 2-(4-methoxy-2-methylphenethyl)-8-pentylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; (2-(2-(1H-indol-5-yl)ethyl)-5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol; N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide; methyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,3-dimethylbenzamide; N-(2-acetamidoethyl)-4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide; 2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,N,3-trimethylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-hydroxyethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-3-methylbenzamide; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(pyrrolidin-1-yl)methanone; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(diethylamino)ethyl)-3-methylbenzamide; (4-(2-(5-amino-8-

methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(4-ethylpiperazin-1-yl)methanone; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(piperazin-1-yl)methanone; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methyl-N-(2-(pyrrolidin-1-yl)ethyl)benzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-aminoethyl)-3-methylbenzamide; 4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N-methylbenzamide; 2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 2-(4-butoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(biphenyl-4-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-((1,3-dihydroisobenzofuran-1-yl)methyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-methylallyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(isopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl propyl carbonate; ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoate; 2-(4-(cyclopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(cyclobutylmethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-1-phenylethanone; 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)ethanol; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-N,N-dimethylacetamide; 8-methyl-2-(2-methyl-4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethanol; diethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonate; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonic acid; 2-(4-butoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol; 2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol; ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoate; 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-

3-methylphenoxy)ethanol; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl ethyl carbonate; methyl 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoate; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoic acid; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)butanoic acid; 2-(4-(isopentyloxy)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl hexyl carbonate; 2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; diethyl 3-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)propylphosphonate; diethyl 3-(2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethoxy)propylphosphonate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl dimethylsulfamate; (5-amino-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 2-(4-(dimethylamino)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone; 2-(4-((dimethylamino)methyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(1-(dimethylamino)ethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone oxime; 8-methyl-2-(4-((methylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzylamino)ethanol; 8-methyl-2-(4-(pyrrolidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3,4-dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)ethanol; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanol; 8-methyl-2-(4-(oxazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propanenitrile; (2R)-2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propan-1-ol; 8-methyl-2-(4-(1-(piperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; ((2S)-1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidin-2-yl)methanol; N^1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^2,N^2-dimethylethane-1,2-diamine; 3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-

yl)ethyl)phenyl)ethylamino)propanoic acid; 8-methyl-2-(4-(1-(4-methylpiperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; N^2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^1,N^1-dimethylpropane-1,2-diamine; 8-methyl-2-(4-(1-(2-(pyridin-4-yl)ethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; N^1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^2,N^2-diethylethane-1,2-diamine; 2-(4-(dimethylamino)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid; 4-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)phenol; 1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2 yl)ethyl)phenyl)ethyl)pyrrolidin-3-ol; and 2-(4-(2-aminopropan-2-yl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine.

[000146] The compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein also includes all suitable isotopic variations of such compounds, and pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions. An isotopic variation of a compound provided herein or a pharmaceutically acceptable salt thereof is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that may be incorporated into the compounds provided herein and pharmaceutically acceptable salts thereof include but are not limited to isotopes of hydrogen, carbon, nitrogen and oxygen such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{35}S, ^{18}F, ^{36}Cl and ^{123}I. Certain isotopic variations of the compounds provided herein and pharmaceutically acceptable salts thereof, for example, those in which a radioactive isotope such as ^{3}H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. In particular examples, ^{3}H and ^{14}C isotopes may be used for their ease of preparation and detectability. In other examples, substitution with isotopes such as ^{2}H may afford certain therapeutic advantages resulting from greater metabolic stability, such as increased in vivo half-life or reduced dosage requirements. Isotopic variations of the compounds, and pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are prepared by conventional procedures using appropriate isotopic variations of suitable reagents.

Processes for Making Compounds of Formula (I)

[000147] General procedures for preparing compounds of Formula (I) are described in the

Examples, *infra*. In the reactions described, reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, may be protected to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice (see e.g., T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry," John Wiley and Sons, 1991).

[000148] In certain embodiments, the compounds of Formula (I) described herein are prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound of Formula (I) with a pharmaceutically acceptable organic acid or inorganic acid. In other embodiments, a pharmaceutically acceptable base addition salt of compounds of Formula (I) described herein is prepared by reacting the free acid form of the compound of Formula (I) with a pharmaceutically acceptable organic base or inorganic base. Alternatively, the salt forms of the compounds of Formula (I) described herein are prepared using salts of the starting materials or intermediates. In certain embodiments, the compounds of Formula (I) described herein are in the form of other salts including, but not limited to, oxalates and trifluoroacetates. In certain embodiments, hemisalts of acids and bases are formed, for example, hemisulphate and hemicalcium salts.

[000149] Such pharmaceutically acceptable acid addition salts of compounds of Formula (I) include, but are not limited to, a hydrobromide, hydrochloride, sulfate, nitrate, succinate, maleate, formate, acetate, adipate, besylatye, bicarbonate/carbonate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, naphthalenesulfonate (e.g. 2-naphthalenesulfonate), hexanoate salt, bisulphate/sulphate, borate, camsylate, cyclamate, edisylate, esylate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, tannate, tosylate, trifluoroacetate and xinofoate salts.

[000150] The organic acid or inorganic acids used to form certain pharmaceutically acceptable acid addition salts of compounds of Formula (I) include, but are not limited to, hydrobromic, hydrochloric, sulfuric, nitric, phosphoric, succinic, maleic, formic, acetic, propionic, fumaric, citric, tartaric, lactic, benzoic, salicylic, glutamic, aspartic, p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, naphthalenesulfonic such as 2-naphthalenesulfonic, or hexanoic

acid.

[000151] Such pharmaceutically acceptable base addition salt of a compound of Formula (I) include, but are not limited to, aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

[000152] In certain embodiments, the free acid or free base forms of the compounds of Formula (I) described herein are prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound Formula (I) in an acid addition salt form is converted to the corresponding free base by treating with a suitable base (by way of example only, an ammonium hydroxide solution, a sodium hydroxide, and the like). For example, a compound of Formula (I) in a base addition salt form is converted to the corresponding free acid by treating with a suitable acid (by way of example only, hydrochloric acid).

[000153] In certain embodiments, compounds of Formula (I) in unoxidized form are prepared from N-oxides of compounds Formula (I) by treating with a reducing agent (by way of example only, sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (by way of example only, acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

[000154] In certain embodiments, prodrug derivatives of compounds Formula (I) are prepared using methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs are prepared by reacting a non-derivatized compound of Formula (I) with a suitable carbamylating agent (by way of example only, 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

[000155] In certain embodiments, compounds of Formula (I) are prepared as protected derivatives using methods known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry," 3rd edition, John Wiley and Sons, Inc., 1999.

[000156] In certain embodiments, compounds of Formula (I) are prepared or formed, as solvates (e.g., hydrates). In certain embodiments, hydrates of compounds of Formula (I) are prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[000157] In certain embodiments, compounds of Formula (I) are prepared as their individual

stereoisomers. In other embodiments, the compounds of Formula (I) described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In certain embodiments, resolution of enantiomers is carried out using covalent diastereomeric derivatives of the compounds of Formula (I), or by using dissociable complexes (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubility, reactivity, etc.) and are readily separated by taking advantage of these dissimilarities. In certain embodiments, the diastereomers are separated by chromatography, or by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions," John Wiley And Sons, Inc., 1981.

[000158] Compounds of Formula (I) are made by processes described herein and as illustrated in the Examples. In certain embodiments, compounds of Formula (I) are made by:

(a) optionally converting a compound of Formula (I) into a pharmaceutically acceptable salt;

(c) optionally converting a salt form of a compound of Formula (I) to a non-salt form;

(d) optionally converting an unoxidized form of a compound of Formula (I) into a pharmaceutically acceptable N-oxide;

(e) optionally converting an N-oxide form of a compound of Formula (I) to its unoxidized form;

(f) optionally resolving an individual isomer of a compound of Formula (I) from a mixture of isomers;

(g) optionally converting a non-derivatized compound of Formula (I) into a pharmaceutically acceptable prodrug derivative; and

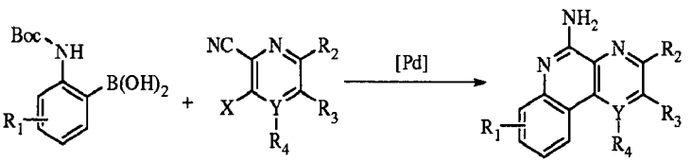
(h) optionally converting a prodrug derivative of a compound of Formula (I) to its non-derivatized form.

[000159] Non-limiting examples of synthetic schemes used to make compounds of Formula (I) described herein are illustrated in reaction schemes (I)-(XI).

[000160] Scheme (I) illustrates the synthesis of benzonaphthyridines (**3**) by coupling substituted or unsubsubstituted 2-(*tert*-butoxycarbonyl-amino)phenylboronic acids (**1**) with substituted or

unsubsubstituted 3-halopicolinonitrile derivatives (**2**) in the presence of a palladium catalyst. By way of example only, the halo moiety of the 3-halopicolinonitrile derivatives is bromo or chloro. The functional groups (R_1, R_2, R_3, R_4) on benzonaphthyridines (**3**) are optionally further modified, as described herein.

Scheme (I)

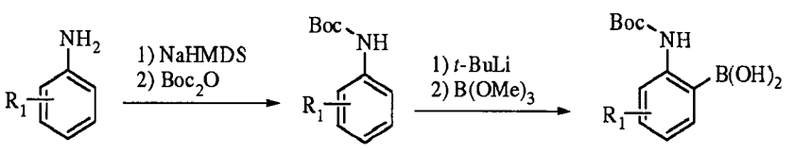


1 **2** **3**

X = Br or Cl
Y = C or N

[000161] In certain embodiments, the phenyl boronic acids used in the synthesis of compounds of Formula (I) were synthesized according to scheme (II). In scheme (II) substituted or unsubsubstituted anilines (**4**) are Boc-protected under basic conditions to give (**5**), and then converted into the boronic acids (**1**) through ortho-lithiation and reaction with trimethyl borate followed by aqueous workup.

Scheme (II)



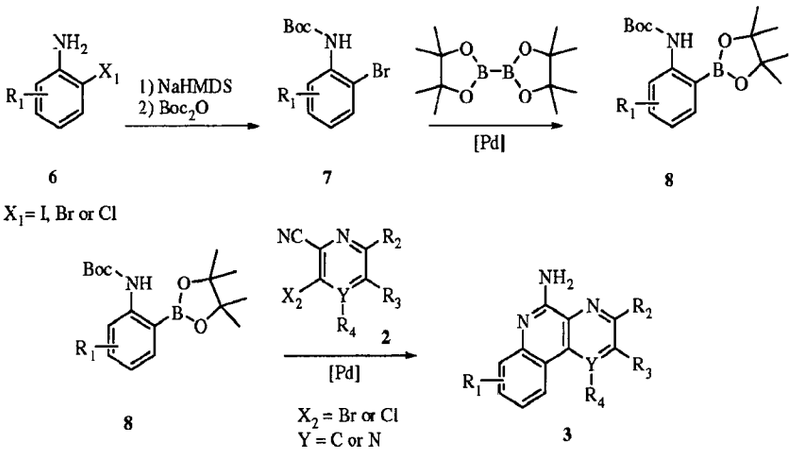
4 **5** **1**

[000162] Boric acids (**1**) are used as in scheme (I) and reacted with substituted or unsubsubstituted cyanopyridines (**2**) to afford substituted or unsubsubstituted benzonaphthyridines (**3**).

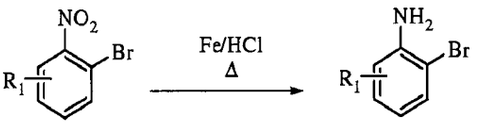
[000163] In certain embodiments, boronic acid equivalents including, but not limited to, substituted or unsubstituted boronate esters were used in the synthesis of compounds of Formula (I). Scheme (III) illustrates the synthesis of such substituted or unsubsubstituted boronate esters (**8**), which were used as boronic acid equivalents in the synthesis of substituted or unsubsubstituted benzonaphthyridines (**3**). In scheme (III) substituted or unsubsubstituted 2-haloanilines (**6**) are Boc-protected under basic conditions to give (**7**), which are then converted into the substituted or unsubsubstituted boronate esters (**8**) using palladium-mediated catalysis. These boronate esters (**8**) are used as in scheme (I) and react with substituted or unsubsubstituted cyanopyridines (**2**) to

afford substituted or unsubsubstituted benzonaphthyridines (**3**).

Scheme (III)

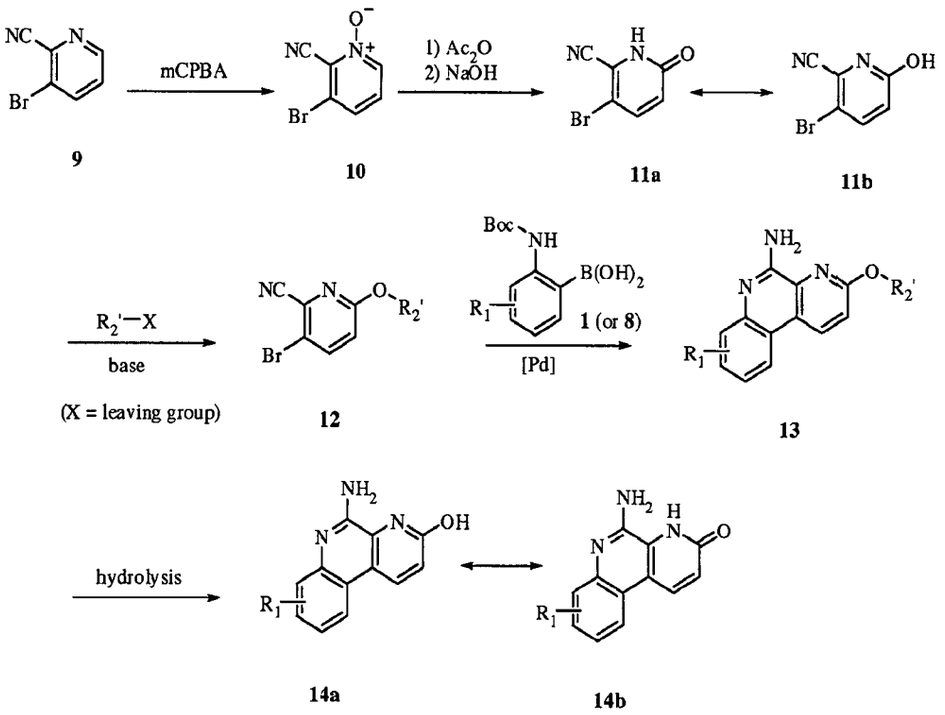


[000164] In certain embodiments, substituted or unsubsubstituted 2-bromoanilines used in scheme (III) were synthesized from their corresponding substituted or unsubsubstituted nitrobenzene compounds as illustrated below:



[000165] In certain embodiments, compounds of Formula (I) having oxygen-linked substituents were synthesized using the methodologies described in scheme (IV).

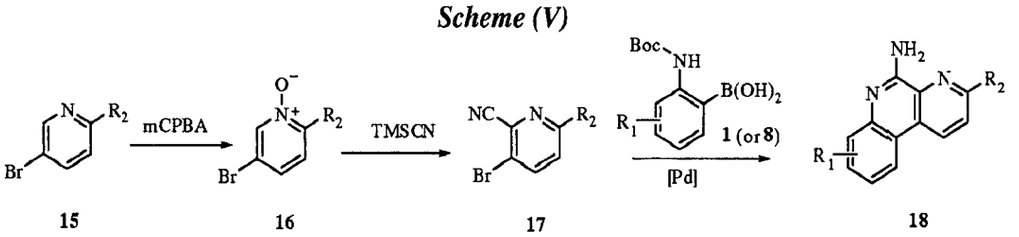
Scheme (IV)



[000166] In scheme (IV) benzonitrile (**9**) is first oxidized to N-oxide (**10**) with meta-chloroperbenzoic acid (mCPBA), and then converted into pyridone (**11**). Under specific basic conditions, the pyridone (**11**) is selectively alkylated on the oxygen to give the alkoxypicolinonitrile (**12**). Using palladium-mediated conditions, as in scheme (I), derivatives of alkoxypicolinonitrile (**12**) are coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give substituted or unsubstituted benzonaphthyridine (**13**) with oxygen-linked substituents. In certain embodiments, the benzonaphthyridine (**13**) with oxygen-linked substituents was hydrolyzed to obtain the corresponding benzonaphthyridone (**14**).

[000167] In other embodiments, compounds of Formula (I) having various substituents were synthesized using the methodologies described in scheme (V).

Scheme (V)

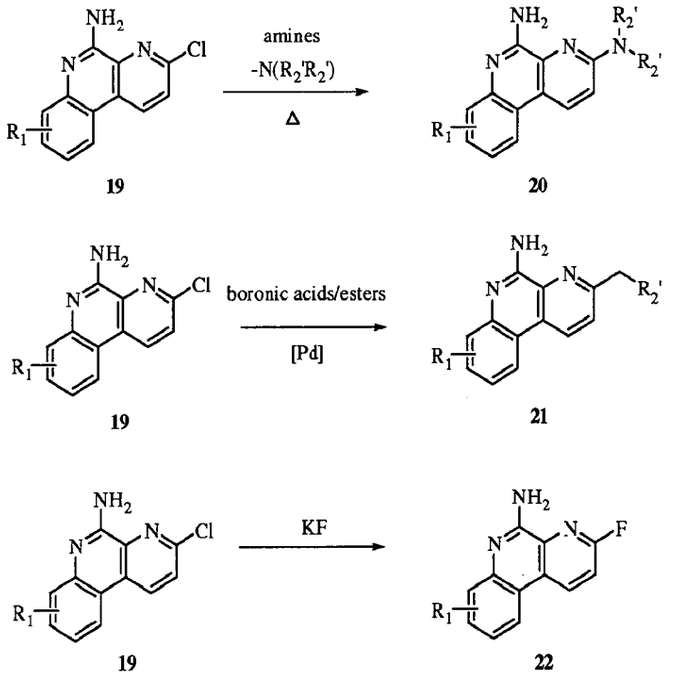


[000168] In scheme (V), 5-bromopyridines (**15**) substituted at the 2-position (shown as R_2 in scheme (V)) are first oxidized by meta-chloroperbenzoic acid (mCPBA) to give the N-oxide **16**,

which are then converted to the benzonitrile (**17**). Using palladium-mediated conditions, as in scheme (I), derivatives of benzonitrile (**17**) are coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give substituted or unsubstituted benzonaphthyridine (**18**) with various substituents in the 3-position. In other embodiments, benzonaphthyridine having various substituents in the 2-position are obtained by starting with 5-bromopyridines substituted at the 3-position.

[000169] In certain embodiments, the substituent in the 3-position of the benzonaphthyridine (**18**) is a chlorine atom, and this 3-chloro-benzonaphthyridine (**19**) is further modified to obtain other substituents at the 3-position of the benzonaphthyridines. Non-limiting examples of such modifications are illustrated in scheme (VI).

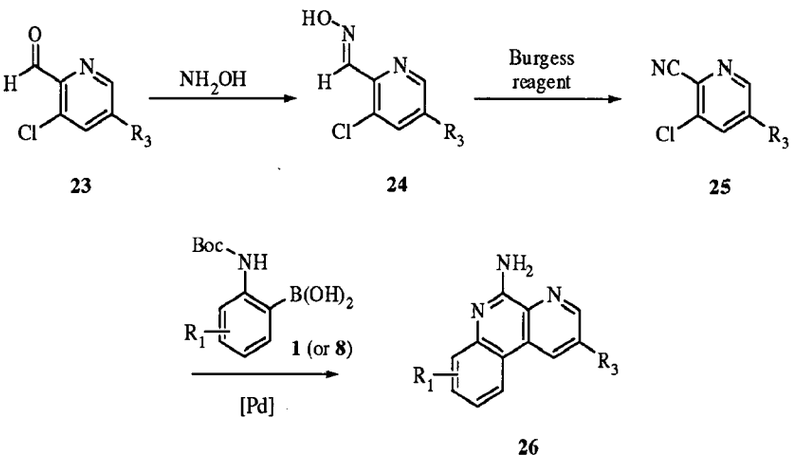
Scheme (VI)



[000170] In certain embodiments, as illustrated in scheme (VI), compounds of Formula (I) having N-linked substituents (derivatives of (**20**)) were obtained via S_NAr reactions by heating such chloro-derivatives (**19**) with various amines. In certain embodiments, as illustrated in scheme (VI), compounds of Formula (I) having carbon-linked substituents (derivatives of (**21**)) were obtained via Suzuki couplings using palladium-mediated conditions with various boronic acids or boronate esters. In certain embodiments, as illustrated in scheme (VI), compounds of Formula (I) were fluorinated by treatment of such chloro-derivatives (**19**) with potassium fluoride to give (3-fluorobenzo[f][1,7]-naphthyridin-5-amine (**22**)).

[000171] In other embodiments, compounds of Formula (I) having various substituents were synthesized using the methodologies described in scheme (VII).

Scheme (VII)

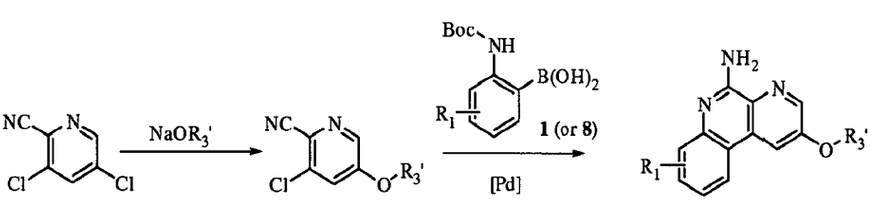


23 24 25 26

[000172] In scheme (VII), 3-chlorobenzaldehyde (**23**) (with a substituent R_3 at the 5-position) is first converted to the corresponding hydroxylamine (**24**), which is then used to make the corresponding nitrile (**25**). Using palladium-mediated conditions, as in scheme (I), derivatives of nitrile (**25**) are coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give the benzonaphthyridine (**26**) with various substituents in the 2-position.

[000173] In other embodiments, certain compounds of Formula (I) having oxygen-linked substituents were synthesized using the methodologies described in scheme (VIII).

Scheme (VIII)



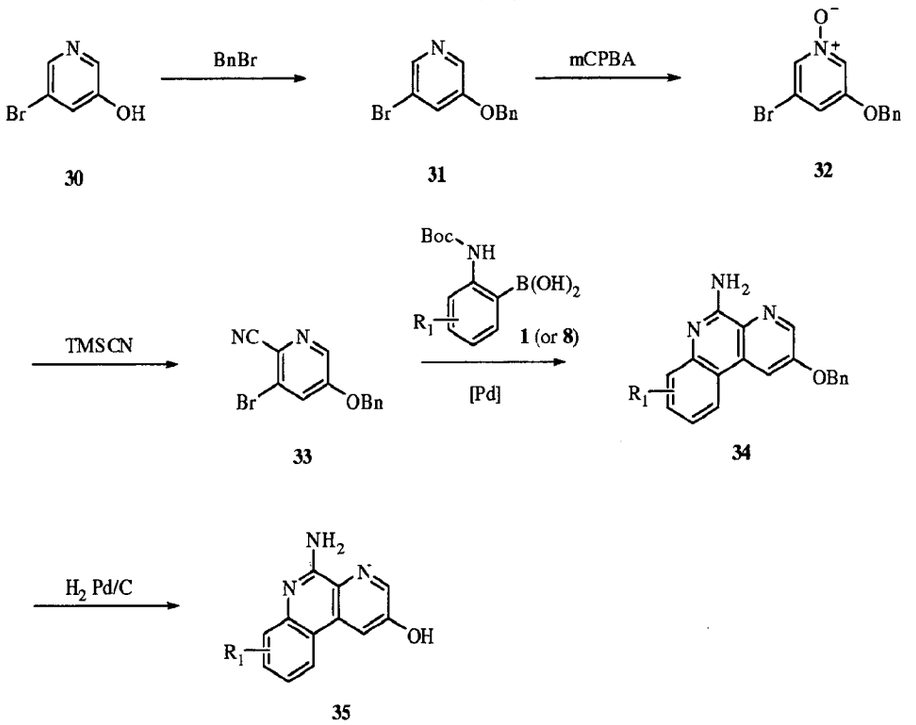
27 28 29

[000174] In scheme (VIII), benzonaphthyridines with various different oxygen-linked R_3 substituents at the 2-position are prepared using a 3,5-dihalopicolinonitrile, such as, by way of example only, 3,5-dichloropicolinonitrile (**27**), which is first mono-substituted with an alkoxy appendage to give the corresponding picolinonitrile (**28**). Then, using palladium-mediated conditions as in scheme (I), derivatives of nitrile (**27**) are coupled with substituted or unsubstituted

boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give the benzonaphthyridine (**29**) with various oxygen –linked substituents in the 2-position.

[000175] In certain embodiments, compounds of Formula (I) having hydroxy substituents, including benzonaphthyridines hydroxy substituents at the 2-position, were prepared using the synthetic route shown in scheme (IX).

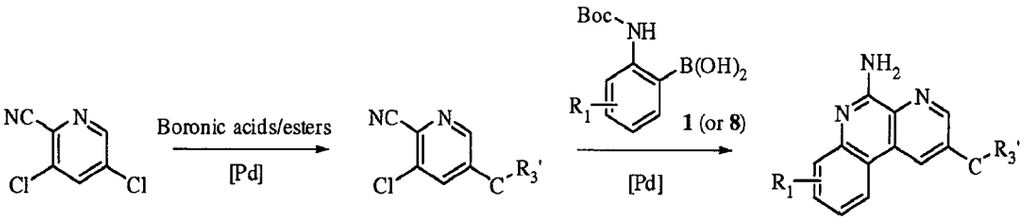
Scheme (IX)



[000176] In scheme (IX), a 5-halopyridin-3-ol such as, by way of example only, 3,5-bromopyridin-3-ol (**30**), is benzyl-protected at the hydroxyl group to give (**31**), which is then converted to the corresponding N-oxide (**32**). The N-oxide (**32**) is further converted into the nitrile (**33**). Then, using palladium-mediated conditions as in scheme (I), derivatives of nitrile (**33**) are coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give the benzonaphthyridine (**34**) which upon hydrogenation gives the benzonaphthyridine (**35**) with a hydroxyl substituent in the 2-position.

[000177] In other embodiments, certain compounds of Formula (I) having carbon-linked substituents, including benzonaphthyridines with various carbon-linked substituents at the 2-position, were prepared using the synthetic route shown in scheme (X).

Scheme (X)

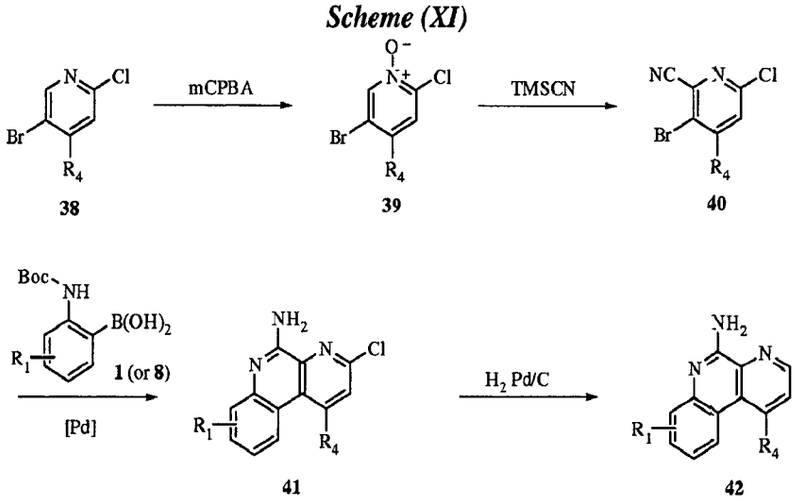


27 36 37

[000178] In scheme (X), a 3,5-dihalopicolinonitrile, such as, by way of example only, 3,5-dichloropicolinonitrile (**27**), is first mono-substituted using one equivalent of boronic acid/ester thereby giving the corresponding picolinonitrile (**36**). Using more vigorous palladium-mediated conditions as in scheme (I), derivatives of nitrile (**36**) are coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give the benzonaphthyridine (**37**) having carbon-linked substituents at the 2-position. In certain embodiments the carbon-linked substituent is an alkene, while in other embodiments such alkenes are further modified by hydrogenation to give benzonaphthyridines with alkyl groups at the 2-position.

[000179] In other embodiments, certain compounds of Formula (I) having various substituents, including benzonaphthyridines with various substituents at the 1-position, were synthesized using the methodologies described in scheme (XI).

Scheme (XI)



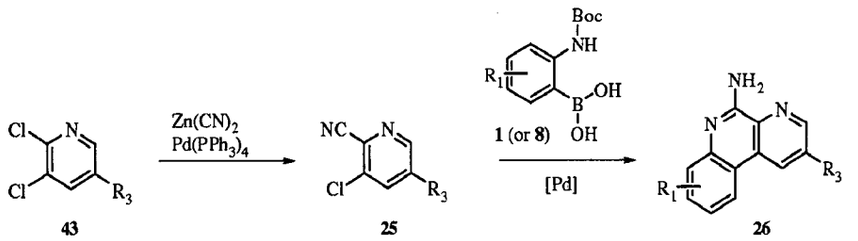
38 39 40 41 42

[000180] In scheme (XI), a 2,5-dihalopyridine substituted at the 4 position such as, by way of example only, 5-bromo-2-chloropyridine (**38**) is first converted to the corresponding N-oxide (**39**), which is then converted to the corresponding nitrile (**40**). Using palladium-mediated conditions as in scheme (I), derivatives of nitrile (**40**) are coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give the benzonaphthyridine (**41**) having

substituents at the 1-position. In certain embodiments, benzonaphthyridine (**41**) is further de-chlorinated to give benzonaphthyridine (**42**).

[000181] In other embodiments, certain compounds of Formula (I) having various substituents, including benzonaphthyridines with various substituents at the 2-position, were synthesized using the methodologies described in scheme (XII).

Scheme (XII)

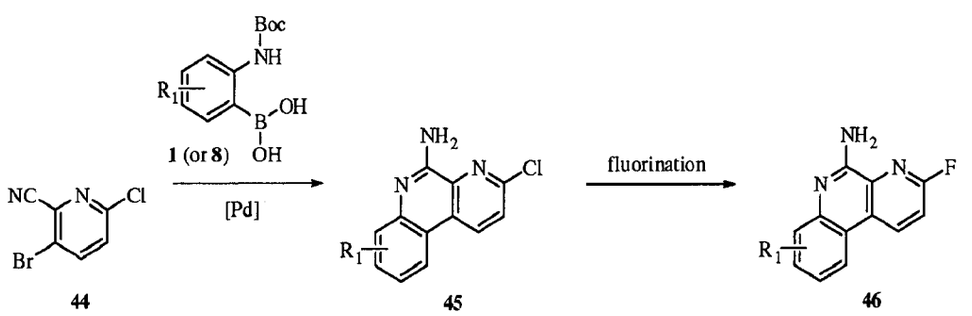


43 25 26

[000182] In scheme (XII), a 2,3-dihalopyridines substituted at the 5 position (**43**), such as, by way of example only, (5,6-dichloropyridin-3-yl)methanol, is first converted to the corresponding nitrile (**25**). Using palladium-mediated conditions as in scheme (I), derivatives of nitrile (**25**) are coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give the benzonaphthyridine (**26**) having substituents at the 2-position.

[000183] Various 3-halo naphthyridines were prepared according to the general methods as exemplified in Scheme XIII.

Scheme (XIII)



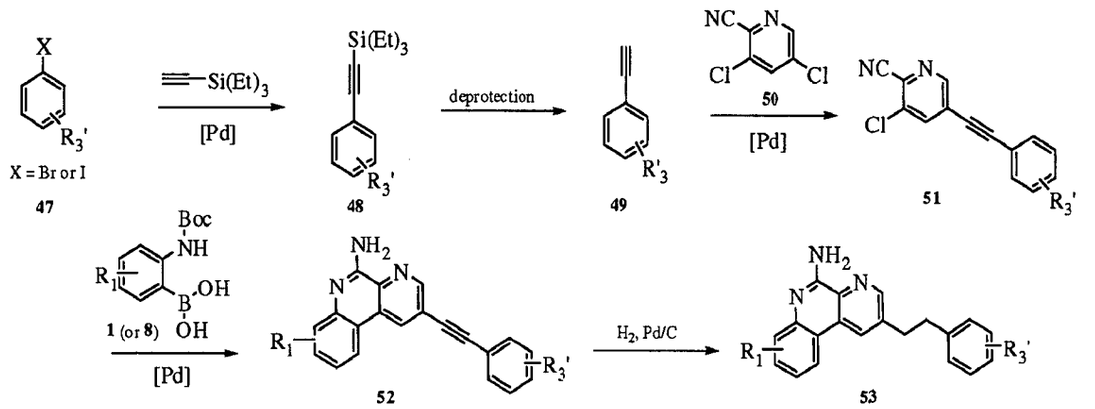
44 45 46

[000184] In scheme (XIII), using palladium-mediated conditions as in scheme (I), a 3,6-dihalo-2-cyanopyridines such as, by way of example only, 3-bromo-6-chloropicolinonitrile is coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give the benzonaphthyridine (**45**) having halogen substitutions at the 3-position. Further halogen exchange of benzonaphthyridine (**45**) gave benzonaphthyridine (**46**) with different halaogen substituents at the 3-position.

[000185] In other embodiments, certain compounds of Formula (I) were synthesized using the

methodologies described in scheme (XIV).

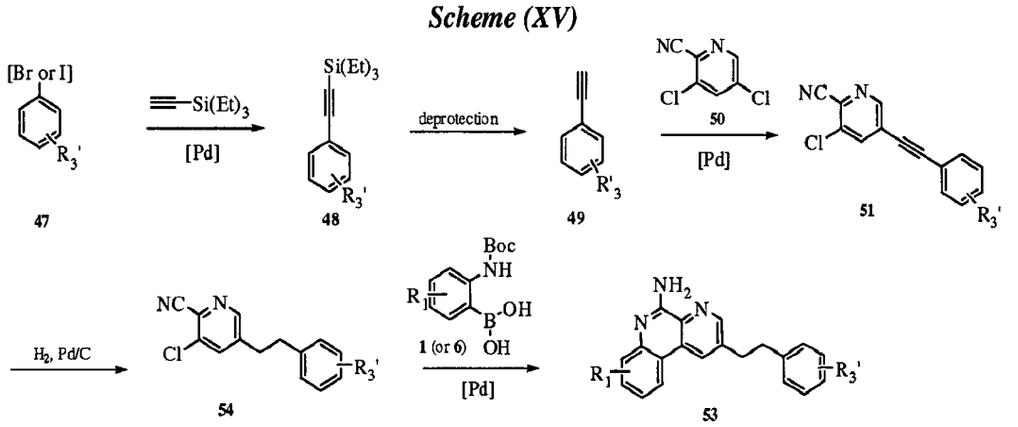
Scheme (XIV)



[000186] In scheme (XIV), aryl bromides or aryl iodides (**47**) substituted with various R_3' groups are coupled with triethyl(ethynyl)silane (or its equivalents) using palladium-mediated conditions to afford **48**. After deprotection of the silyl protection group, acetylene derivatives (**49**) are coupled with 3,5-dichloropicolinonitrile (**50**) using palladium-mediated conditions to afford 3-chloro-2-cyanopyridines (**51**). Derivatives of **51** such as, by way of example only, 3-chloro-5-(phenylethynyl)picolinonitrile is coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give the benzonaphthyridine (**52**). Compound **52** is then subjected under hydrogenation conditions to give benzonaphthyridines **53** with different substitutents at the R_3' position.

[000187] In other embodiments, certain compounds of Formula (I) were synthesized using the methodologies described in scheme (XV).

Scheme (XV)

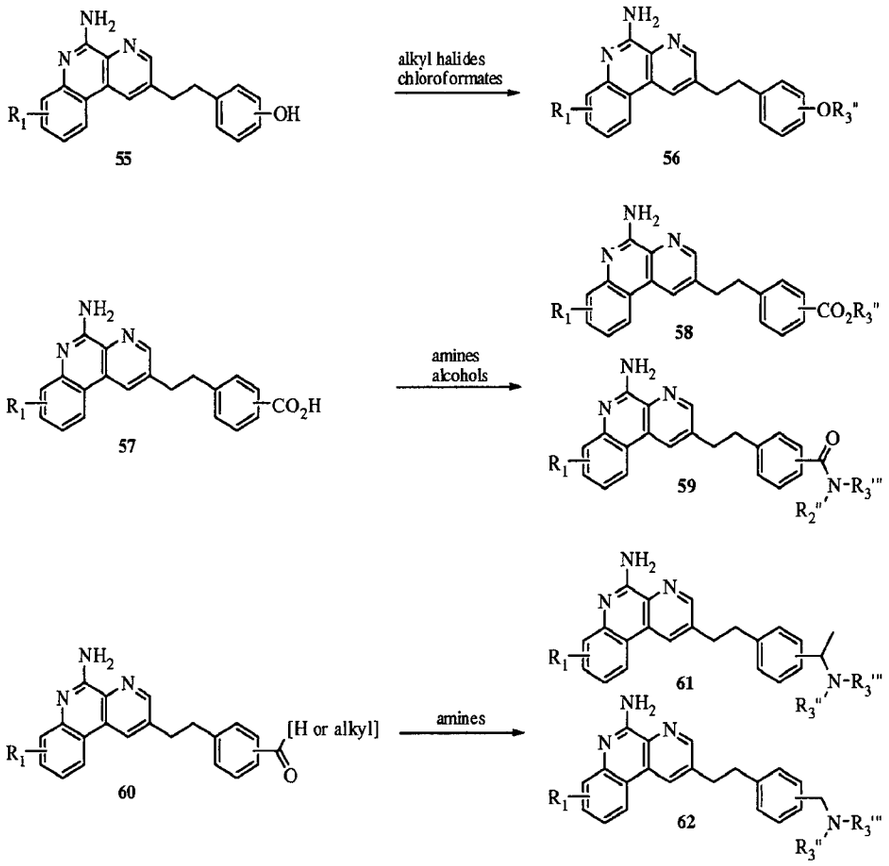


[000188] In scheme (XV), aryl bromides or aryl iodides (**47**) substituted with various R_3' groups are coupled with triethyl(ethynyl)silane (or its equivalents) using palladium-mediated conditions to

afford **48**. After deprotection of the silyl protection group, acetylene derivatives (**49**) are coupled with 3,5-dichloropicolinonitrile (**50**) using palladium-mediated conditions to afford 3-chloro-2-cyanopyridines (**51**). Derivatives of **51** such as, by way of example only, 3-chloro-5-(phenylethynyl)picolinonitrile is reduced to the corresponding 3-chloro-5-phenethylpicolinonitrile (**54**) under hydrogenation conditions. Compound **54** is coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give benzonaphthyridines **53** with different substitutents at the R_3' position.

[000189] Benzonaphthyridines with various substitutions can be further converted into other functional groups using standard organic transformations. In certain embodiments, certain compounds of Formula (I) were synthesized using the methodologies described in scheme (XVI).

Scheme (XVI)

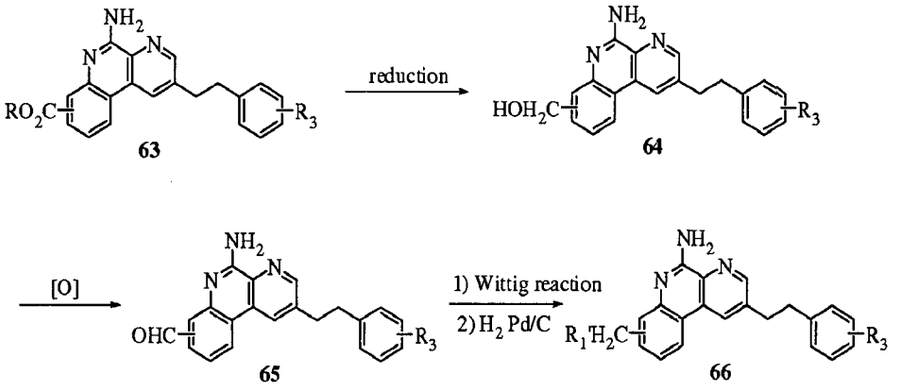


[000190] By way of example, in Scheme (XVI), benzonaphthyridines bearing a hydroxyl group (**55**) are converted to the corresponding ethers or carbonates (**56**). For example, benzonaphthyridines bearing a carboxylic acid group (**57**) are converted to the corresponding esters (**58**) or amides (**59**). For example, benzonaphthyridines bearing an aldehyde or ketone group (**60**) are converted to the corresponding amines (**61** or **62**). These benzonaphthyridines can

be further modified using the standard organic transformations.

[000191] In certain embodiments, certain compounds of Formula (I) were synthesized using the methodologies described in scheme (XVII).

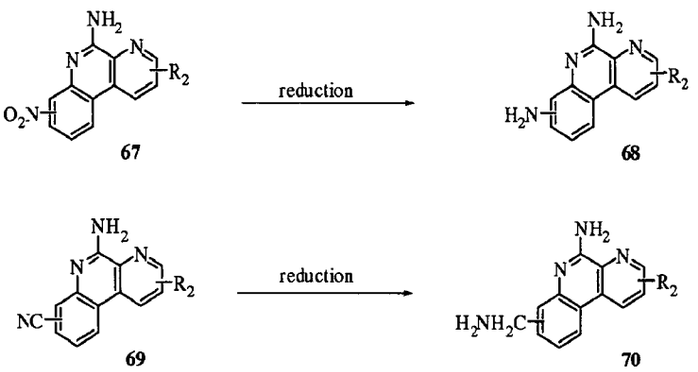
Scheme (XVII)



[000192] In scheme (XVII), benzonaphthyridines with various substitutions are further converted to different functional groups through standard organic transformations. For example, benzonaphthyridines bearing an ester group (**63**) are converted to the corresponding alcohol (**64**) by reduction using standard reducing agents. Compound **64** is oxidized to the corresponding aldehyde (**65**), which is further alkylated by a Wittig reaction followed by hydrogenation to give derivatives **66**. These benzonaphthyridines can be further modified using the standard organic transformations.

[000193] In certain embodiments, certain compounds of Formula (I) were synthesized using the methodologies described in scheme (XVIII).

Scheme (XVIII)

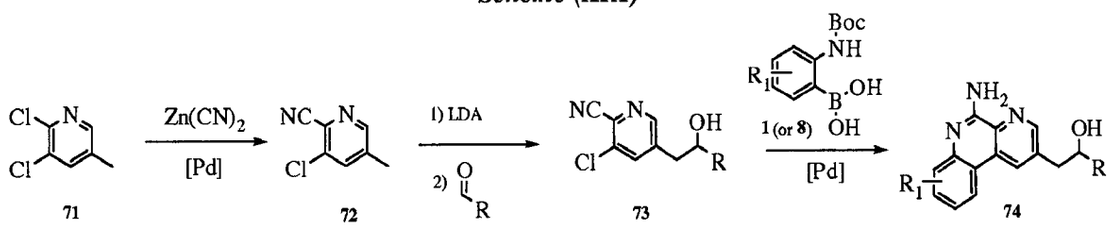


[000194] In scheme (XVIII), benzonaphthyridines with various substitutions are further converted to different functional groups through standard organic transformations. For example, benzonaphthyridines bearing a nitro group (**67**) or a cyano group (**69**) are converted to the corresponding amine (**68**) or methyl amine (**70**) by reduction using standard reducing agents.

These benzonaphthyridines can be further modified using the standard organic transformations.

[000195] In certain embodiments, certain compounds of Formula (I) were synthesized using the methodologies described in scheme (XIX).

Scheme (XIX)



[000196] In scheme (XIX), 2,3-dichloro-5-methylpyridine (**71**) is converted to the corresponding nitrile (**72**). Alcohol **73** is formed under Aldol condensation conditions, wherein compound **72** reacts with an aldehyde or ketone. Derivatives of **73** are then coupled with boronic acids (**1**) or boronate esters (**8**) to give the benzonaphthyridine (**74**).

[000197] The following examples are offered to illustrate, but not to limit, the compounds of Formula (I) provided herein, and the preparation of such compounds.

Pharmacology and Utility

[000198] When a foreign antigen challenges the immune system it responds by launching a protective response that is characterized by the coordinated interaction of both the innate and acquired immune systems. These two interdependent systems fulfill two mutually exclusive requirements: speed (contributed by the innate system) and specificity (contributed by the adaptive system).

[000199] The innate immune system serves as the first line of defense against invading pathogens, holding the pathogen in check while the adaptive responses are matured. It is triggered within minutes of infection in an antigen-independent fashion, responding to broadly conserved patterns in the pathogens (though it is not non-specific, and can distinguish between self and pathogens). Crucially, it also generates the inflammatory and co-stimulatory milieu (sometimes referred to as the danger signal) that potentiates the adaptive immune system and steers (or polarizes it) towards the cellular or humoral responses most appropriate for combating the infectious agent. The development of TLR modulators for therapeutic targeting of innate immunity has been reviewed (see Nature Medicine, 2007, 13, 552-559; Drug Discovery Today: Therapeutic Stategies, 2006, 3, 343-352 and Journal of Immunology, 2005, 174, 1259-1268).

[000200] The adaptive response becomes effective over days or weeks, but ultimately provides the fine antigenic specificity required for complete elimination of the pathogen and the generation

of immunologic memory. It is mediated principally by T and B cells that have undergone germline gene rearrangement and are characterized by specificity and long-lasting memory. However, it also involves the recruitment of elements of the innate immune system, including professional phagocytes (macrophages, neutrophils etc.) and granulocytes (basophils, eosinophils etc.) that engulf bacteria and even relatively large protozoal parasites. Once an adaptive immune response has matured, subsequent exposure to the pathogen results in its rapid elimination due to highly specific memory cells have been generated that are rapidly activated upon subsequent exposure to their cognate antigen.

[000201] Autoimmune diseases, are defined by (i) humoral or autoantibody response to a self antigen (by way of example only, Graves' primary hyperthyroidism with antibodies to the TSH receptor), or (ii) cellular response wherein immune cells destroy nonimmune cells from which the self-antigen is derived (by way of example only, the thyrocyte (Hashimoto's thyroiditis) or pancreatic β-islet cell (Type 1 diabetes). Many autoimmune diseases are a combination of both phenomena, for instance, Hashimoto's and Type 1 diabetes also have auto-antibodies, anti-thyroid peroxidase (TPO) or anti-glutamic acid decarboxylase (GAD)/Islet Cell. Autoimmune diseases often have an inflammatory component including, but not limited to, increases in adhesion molecules (by way of example only, vascular cell adhesion molecule-1 (VCAM-1), and altered leukocyte adhesion to the vasculature such as, by way of example only, colitis, systemic lupus, systemic sclerosis, and the vascular complications of diabetes.

[000202] Toll-like receptors (TLRs) are type-I transmembrane proteins characterized by an extracellular N-terminal leucine-rich repeat (LRR) domain, followed by a cysteine-rich region, a TM domain, and an intracellular (cytoplasmic) tail that contains a conserved region named the Toll/IL-1 receptor (TIR) domain. TLRs are pattern recognition receptors (PRR) that are expressed predominantly on immune cells including, but not limited to, dendritic cells, T lymphocytes, macrophages, monocytes and natural killer cells. The LLR domain is important for ligand binding and associated signaling and is a common feature of PRRs. The TIR domain is important in protein-protein interactions and is associated with innate immunity. The TIR domain also unites a larger IL-1 R/TLR superfamily that is composed of three subgroups. Members of the first group possess immunoglobin domains in their extracellular regions and include IL-1 and IL-18 receptors and accessory proteins as well as ST2. The second group encompasses the TLRs. The third group includes intracellular adaptor proteins important for signaling.

[000203] TLRs are a group of pattern recognition receptors which bind to pathogen-associated

molecular patterns (PAMPS) from bacteria, fungi, protozoa and viruses, and act as a first line of defense against invading pathogens. TLRs are essential to induce expression of genes involved in inflammatory responses, and TLRs and the innate immune system are a critical step in the development of antigen-specific acquired immunity.

[000204] Adaptive (humoral or cell-mediated) immunity is associated with the TLR signal mechanism of innate immunity. Innate immunity is a protective immune cell response that functions rapidly to fight environmental insults including, but not limited to, bacterial or viral agents. Adaptive immunity is a slower response, which involves differentiation and activation of naive T lymphocytes into T helper 1 (Th1) or T helper 2 (Th2) cell types. Th1 cells mainly promote cellular immunity, whereas Th2 cells mainly promote humoral immunity. Though primarily a host protective system, pathologic expression of the innate immunity signals emanating from the TLR pathway are implicated in initiating autoimmune-inflammatory diseases.

[000205] All TLRs appear to function as either a homodimer or heterodimer in the recognition of a specific, or set of specific, molecular determinants present on pathogenic organisms including bacterial cell-surface lipopolysaccharides, lipoproteins, bacterial flagellin, DNA from both bacteria and viruses and viral RNA. The cellular response to TLR activation involves activation of one or more transcription factors, leading to the production and secretion of cytokines and co-stimulatory molecules such as interferons, TNF-, interleukins, MIP-1 and MCP-1 which contribute to the killing and clearance of the pathogenic invasion.

[000206] TLR spatial expression is coincident with the host's environmental interface. While only a few other Toll-like proteins have been cloned in *Drosophila*, the human TLR family is composed of at least 11 members, TLR1 through TLR11, that elicit overlapping yet distinct biological responses due to differences in cellular expression and signaling pathways they initiate. Each of the TLRs is expressed on a different subset of leukocytes and each of the TLRs is specific in its expression patterns and PAMP sensitivities and detects different subsets of pathogens allowing vigilant surveillance by the immune system.

Toll-like Receptor 1 (TLR1)

[000207] TLR1 maps to chromosome 4p14 and its sequence encodes a putative 786 amino acid (aa) protein with 18 N-terminal LRRs and a calculated molecular weight of 84 kDa. TLR1 is most closely related to TLR6 and TLR10 with 68% and 48% overall (aa) sequence identity, respectively.

[000208] TLR1 mRNA is ubiquitously expressed and found at higher levels than the other TLRs. Of the major leukocyte populations, TLR1 is most highly expressed by monocytes, but is also

expressed by macrophages, dendritic cells, polymorphonuclear leukocytes, B, T, and NK cells. *In vivo*, two different sized transcripts for TLR1 are observed suggesting that the mRNA is alternatively spliced to generate two different forms of the protein. *In vitro*, TLR1 mRNA and protein expression is upregulated in monocytic leukemic (THP-1) cells upon PMA-induced differentiation. TLR1 expression is upregulated by autocrine IL-6, and is also elevated by IFN-γß, IL-10, and TNF-α. However, TLR1 level is unaffected by exposure to both Gram-positive and Gram-negative bacteria. *Ex vivo*, both monocyte and granulocyte TLR1 expression is downregulated after exposure to Gram-negative bacteria. TLR1 forms a heterodimer with TLR2. TLR1 also heterodimerizes with TLR4, which inhibits TLR4 activity.

Toll-like Receptor 2 (TLR2)

[000209] TLR2 maps to chromosome 4q31-32 and encodes a putative 784 (aa) protein with 19 N-terminal LLRs and a calculated molecular weight of 84 kDa. TLR2 is most closely related to TLR6 with 31% overall (aa) sequence identity.

[000210] TLR2 mRNA expression is observed in brain, heart, lung, and spleen tissues and is highest in PBLs, specifically those of myelomonocytic origin. *In vivo*, two different sized transcripts for TLR2 are observed suggesting that the mRNA is alternatively spliced. *In vitro*, TLR2 mRNA and protein expression is upregulated in monocytic leukemic (THP-1) cells upon PMA-induced differentiation. TLR2 is upregulated by autocrine IL-6 and TNF-α, IL-1β, and IL-10. TLR2 mRNA expression is elevated after exposure to both Gram-positive and Gram-negative bacteria. TLR2 forms heterodimers with TLR1, TLR6, and possibly TLR10, where each complex is particularly sensitive to subsets of TLR2-associated PAMPs. TLR2 complexes recognize a wide range of PAMPs, mostly from bacteria. These include, but are not limited to, lipoarabinomannan (LAM), lipopolysaccharide (LPS), lipoteichoic acid (LTA), peptidoglycan (PGN), and other glycolipids, glycoproteins, and lipoproteins. TLR2 complexes are also capable of detecting viruses, including but not limited to, measles virus (MV), human cytomegalovirus (HCMV), and hepatitis C virus (HCV) and fungal PAMPs, including but not limited to, zymosan. TLR2 recognizes a variety of lipoproteins/lipopeptides from various pathogens such as, by way of example only, Gram-positive bacteria, mycobacteria, Trypanosoma cruzi, fungi and Treponema. In addition, TLR2 recognizes LPS preparations from non-enterobacteria such as, by way of example only, Leptospira interrogans, Porphyromonas gingivalis and Helicobacter pylori. TLR2 complexes are capable of both detection of non-self patterns and detecting altered self patterns, such as those displayed by necrotic cells. TLR2 is recruited to phagosomes and is involved in the internalization of microbial products by cells.

Toll-like Receptor 3 (TLR3)

[000211] TLR3 maps to chromosome 4q35 and its sequence encodes a putative 904 (aa) protein with 24 N-terminal LRRs and a calculated molecular weight of 97 kDa. TLR3 is most closely related to TLR5, TLR7, and TLR8, each with 26% overall (aa) sequence identity.

[000212] TLR3 mRNA is expressed at highest levels in the placenta and pancreas. TLR3 is expressed by dendritic cells, T and NK cells. *In vivo*, two different sized transcripts for TLR3 are observed suggesting that the mRNA is alternatively spliced to generate two different forms of the protein. *In vitro*, PMA-differentiated THP-1 TLR3 is moderately upregulated by autocrine IFN-γ, IL-1ß, IL-6, IL-10, and TNF-α. TLR3 mRNA is elevated after exposure to Gram-negative bacteria and to an even greater extent in response to Gram-positive bacteria. *Ex vivo*, TLR3 expression is elevated in both monocytes and granulocytes upon exposure to Gram-negative bacteria. TLR3 forms a homodimer and recognizes viral double stranded RNA (dsRNA). While it is generally assumed that TLRs are expressed on the cell surface, however those TLRs sensitive to internal PAMPs, such as dsRNA in the case of TLR3, are localized intracellularly in the lysosomal compartment.

Toll-like Receptor 4 (TLR4)

[000213] TLR4 maps to chromosome 9q32-33, and shows a high degree of similarity to dToll over the entire (aa) sequence. The TLR4 sequence encodes an 839 (aa) protein with 22 N-terminal LRR regions and a calculated molecular weight of 90 kDa. TLR4 is most closely related to TLR1 and TLR6 each with 25% overall (aa) sequence identity.

[000214] *In vivo*, TLR4 mRNA is expressed as a single transcript, and found at highest levels in spleen and PBLs. Of the PBL populations, TLR4 is expressed by B cells, dendritic cells, monocytes, macrophages, granulocytes, and T cells. TLR4 is also expressed in myelomonocytic cells and is highest in mononuclear cells. *In vitro*, TLR4 mRNA and protein expression is upregulated in THP-1 cells upon PMA-induced differentiation. TLR4 is moderately upregulated by autocrine IFN-γ, IL-1β. TLR4 mRNA expression in THP-1 cells is unaffected by exposure to both Gram-positive and Gram-negative bacteria. *Ex vivo*, granulocyte, and monocyte, TLR4 expression is upregulated upon exposure to Gram-negative bacteria.

[000215] TLR4 forms a homodimer and requires the extracellular association of an additional component, MD-2. Although TLR2 complexes are capable of recognizing lipopolysaccharide (LPS), TLR4 is generally considered the LPS receptor. MD-2-associated TLR4 homodimers do not bind LPS directly, however. LPS must first be bound by the soluble LPS binding protein (LBP). LBP is then bound by either soluble or GPI-linked CD14. Additional cell type-dependent

components required for LPS detection by TLR4 include CXCR4, GDF-5, CD55, various heat shock proteins (HSPs), and complement receptors (CRs). The TLR4 complex also recognizes a few other bacterial PAMPs including LTA. Further, the TLR4 complex recognizes viruses including respiratory syncytial virus (RSV), hepatitis C virus (HCV), and mouse mammary tumor virus (MMTV). The TLR4 complex can also recognize endogenous ligands, for example, heat shock proteins (HSP60 and HSP70), fibrinogen, domain A of fibronectin, oligosaccharides of hyaluronic acid, heparan sulfate, surfactant protein A (SP-A), and β-defensins. TLR4 also forms heterodimers both with TLR5, which enhances its activity, and also with TLR1, which inhibits its activity.

Toll-like Receptor 5 (TLR5)

[000216] TLR5 maps to chromosome 1q41-42, and the gene encodes a putative 858 (aa) protein with a calculated molecular weight of 91 kDa. It is most closely related to TLR3 with 26% overall (aa) sequence identity.

[000217] *In vivo*, TLR5 mRNA is expressed as a single transcript in ovary, prostate, and PBLs. TLR5 is expressed by several PBL populations with the highest expression found in monocytes. TLR5 is also expressed on the basolateral side of intestinal epithelial cells and intestinal endothelial cells of the subepithelial compartment. *In vitro*, TLR5 is upregulated in PMA-differentiated THP-1 cells by autocrine IL-6, IL-10, and TNF-α, but is also elevated by IFN-γβ. TLR5 mRNA expression is elevated after exposure to both Gram-positive and Gram-negative bacteria. *Ex vivo*, granulocyte and monocyte TLR5 expression is downregulated upon exposure to Gram-negative bacteria. TLR5 forms a homodimer as well as a heterodimer with TLR4. Both complexes function to recognize the Flagellin protein of flagellated bacteria. Expression of human TLR5 in CHO cells confers response to flagellin, a monomeric constituent of bacterial flagella. Flagellin activates lung epithelial cells to induce inflammatory cytokine production. A stop codon polymorphism in TLR5 has been associated with susceptibility to pneumonia caused by the flagellated bacterium Legionella pneumophila.

Toll-like Receptor 6 (TLR6)

[000218] TLR6 maps to chromosome 4p14, and the TLR6 sequence encodes a 796 (aa) protein containing 20 N-terminal LRR motifs with a calculated molecular weight of 91 kDa. TLR6 is most closely related to TLR1, TLR10, and TLR2 with 68%, 46%, and 31% overall (aa) sequence identity, respectively.

[000219] *In vivo*, TLR6 transcript is observed in thymus, spleen, and lung. TLR6 mRNA expression is highest in B cells and monocytes. *In vitro*, TLR6 mRNA expression is upregulated in

THP-1 cells upon PMA-induced differentiation. TLR6 is moderately upregulated by autocrine IFN-γ, IL-1β. However, TLR6 mRNA expression in THP-1 cells is unaffected by exposure to both Gram-positive and Gram-negative bacteria. *Ex vivo*, monocyte andgranulocyte TLR6 expression is downregulated upon exposure to Gram-negative bacteria. TLR6 forms a heterodimer with TLR2. Like TLR1, TLR6 is thought to specify or enhance the PAMP sensitivity of TLR2 and contribute to its signaling capabilities through heterodimerization.

Toll-like Receptor 7 (TLR7)

[000220] TLR7 maps to human chromosome Xp22, and the TLR7 sequence encodes a 1049 (aa) protein containing 27 N-terminal LRRs with a calculated molecular weight of 121 kDa. TLR7 is most closely related to TLR8 and TLR9 with 43% and 36% overall (aa) sequence identity, respectively.

[000221] *In vivo*, TLR7 mRNA is expressed in lung, placenta, spleen, lymph node, and tonsil. TLR7 mRNA expression is highest in monocytes, B cells, and plasmocytoid dendritic cells. *In vitro*, TLR7 mRNA expression is upregulated in THP-1 cells upon PMA-induced differentiation. TLR7 is highly upregulated by exposure to IL-6 and to a slightly lesser extent by autocrine IFN-γ, IL-1β. TLR7 mRNA expression in THP-1 cells is elevated after exposure to both Gram-positive and Gram-negative bacteria. *Ex vivo*, expression of TLR7 is elevated after exposure to both Gram-positive and Gram-negative bacteria in monocytes and to a greater degree in granulocytes. TLR7 is expressed in the endosome. The role of TLR7, is to detect the presence of "foreign" single-stranded RNA within a cell, as a means to respond to viral invasion. TLR7 is a structurally highly conserved protein which recognizes guanosine- or uridine-rich, single-stranded RNA (ssRNA) from viruses such as human immunodeficiency virus, vesicular stomatitis virus and influenza virus

Toll-like Receptor 8 (TLR8)

[000222] TLR8 maps to chromosome Xp22, and the TLR8 sequence encodes a 1041 (aa) protein containing 26 N-terminal LRRs with a calculated molecular weight of 120 kDa. TLR8 is most closely related to TLR7 and TLR9 with 43% and 35% overall (aa) sequence identity, respectively.

[000223] *In vivo*, TLR8 mRNA is expressed in lung, placenta, spleen, lymph node, bone marrow, and PBLs, with highest expression found in cells of myeloid origin, such as monocytes, granulocytes and myeloid dendritic cells. *In vitro*, TLR8 mRNA expression is upregulated in THP-1 cells upon PMA-induced differentiation. TLR8 is highly upregulated by autocrine IL-1β, IL-6, IL-10, and TNF-α, and is even more enhanced by exposure to IFN-γ. TLR8 mRNA expression in THP-1 cells is elevated after exposure to both Gram-positive and Gram-negative bacteria. *Ex vivo*, monocyte TLR8 expression increases while granulocyte expression decreases on exposure to

Gram-negative bacteria. TLR8 is expressed in the endosome. The role of TLR8 is to detect the presence of "foreign" single-stranded RNA within a cell, as a means to respond to viral invasion. TLR8 is a structurally highly conserved protein which recognizes guanosine- or uridine-rich, single-stranded RNA (ssRNA) from viruses such as human immunodeficiency virus, vesicular stomatitis virus and influenza virus.

Toll-like Receptor 9 (TLR9)

[000224] TLR9 maps to chromosome 3p21, and the TLR9 sequence encodes a 1032 (aa) protein containing 27 N-terminal LRRs with a calculated molecular weight of 116 kDa. TLR9 is most closely related to TLR7 and TLR8 with 36% and 35% overall (aa) sequence identity, respectively.

[000225] *In vivo*, TLR9 mRNA is expressed in spleen, lymph node, bone marrow, and PBLs. Specifically, TLR9 mRNA is expressed at the highest levels in B cells and dendritic cells. *In vitro*, TLR9 is moderately upregulated by autocrine IFN-γ, IL-1ß, IL-6, IL-10, and TNF-α in PMA-differentiated THP-1 cells. TLR9 mRNA expression in THP-1 cells is unaffected by exposure to both Gram-positive and Gram-negative bacteria. *Ex vivo*, TLR9 expression in monocytes and particularly in granulocytes is downregulated in response to Gram-negative bacteria. TLR9 forms a homodimer and recognizes unmethylated bacterial DNA. TLR9 is involved in the inflammatory response to bacterial DNA and oligonucleotides that contain unmethylated CpG DNA sequences. TLR9 is localized internally, perhaps in lysosomic or endocytic compartments where it would more likely encounter PAMPs including unmethylated CpG DNA sequences.

[000226] TLR9 is a receptor for CpG DNA, and recognizes bacterial and viral CpG DNA. Bacterial and viral DNA contains unmethylated CpG motifs, which confer its immunostimulatory activity. In vertebrates, the frequency of CpG motifs is severely reduced and the cytosine residues of CpG motifs are highly methylated, leading to abrogation of the immunostimulatory activity. Structurally, there are at least two types of CpG DNA: B/K-type CpG DNA is a potent inducer of inflammatory cytokines such as IL-12 and TNF-α; A/D-type CpG DNA has a greater ability to induce IFN-α production from plasmacytoid dendritic cells (PDC). TLR9 is also involved in pathogenesis of autoimmune disorders, and may be important in Graves' autoimmune hyperthyroidism and production of rheumatoid factor by auto-reactive B cells. Similarly, internalization by the Fc receptor can cause TLR9 mediated PDC induction of IFN-α by immune complexes containing IgG and chromatin, which are implicated in the pathogenesis of systemic lupus erythematosus (SLE). TLR9 is involved in the pathogenesis of several autoimmune diseases through recognition of the chromatin structure.

Toll-like Receptor 10 (TLR10)

[000227] The TLR10 sequence encodes a putative 811 (aa) protein with molecular weight of 95 kDa. TLR10 is most closely related to TLR1 and TLR6 with 48% and 46% overall (aa) identity, respectively.

[000228] *In vivo*, TLR10 mRNA expression is highest in immune system-related tissues including spleen, lymph node, thymus, and tonsil. TLR10 mRNA is most highly expressed on B cells and plasmacytoid dendritic cells (PDCs). *In vitro*, TLR10 is moderately upregulated by autocrine IFN-γ, IL-1β, IL-6, IL-10, and TNF-α in PMA-differentiated THP-1 cells. TLR10 mRNA expression in THP-1 cells is elevated after exposure to both Gram-positive and Gram-negative bacteria. *Ex vivo*, monocyte TLR10 expression increases, while granulocyte expression decreases on exposure to Gram-negative bacteria.

Toll-like Receptor 11 (TLR11)

[000229] TLR11 is expressed in bladder epithelial cells and mediate resistance to infection by uropathogenic bacteria in mouse.

[000230] As presented above, TLR2 and TLR4 recognize Gram-positive and Gram-negative bacterial cell wall products, respectively; TLR5 recognizes a structural epitope of bacterial flagellin; TLR3, TLR7, TLR8, and TLR9 recognize different forms of microbial-derived nucleic acid.

[000231] The TIR domains interact with several TIR domain-containing adaptor molecules (MyD88), TIR domain-containing adaptor protein (TIRAP), TIR domain-containing adaptor-inducing IFN-β (TRIF), and TRIF-related adaptor molecule (TRAM) which activate a cascade of events resulting in transcription factor induction.

TLR Signaling Pathways.

[000232] TLRs are distributed throughout the cell. TLR1, TLR2, TLR3 and TLR4 are expressed on the cell surface, whereas, TLR3, TLR7, TLR8 and TLR9 are expressed in intracellular compartments such as endosomes. TLR3-, TLR7- or TLR9-mediated recognition of their ligands require endosomal maturation and processing. When macrophages, monocytes, dendritic cells or nonimmune cells that become antigen presenting cells engulf bacteria by phagocytosis, the bacteria degrade and CpG DNA is release into phagosomes-lysosomes or in endosomes-lysosomes wherein they can interact with TLR9 that has been recruited from the endoplasmic reticulum upon non-specific uptake of CpG DNA. Furthermore, when viruses invade cells by receptor-mediated endocytosis, the viral contents are exposed to the cytoplasm by fusion of the viral membrane with

the endosomal membrane. This results in exposure of TLR ligands such as dsRNA, ssRNA and CpG DNA to TLR9 in the phagosomal/lysosomal or endosomal/lysosomal compartments.

[000233] In the signaling pathways downstream of the TIR domain, a TIR domain-containing adaptor, MyD88, is essential for induction of inflammatory cytokines such as TNF-α and IL-12 through all TLRs. Although TIR domain-containing adaptor molecules (MyD88) are common to all TLRs, individual TLR signaling pathways are divergent and activation of specific TLRs leads to slightly different patterns of gene expression profiles. By way of example only, activation of TLR3 and TLR4 signaling pathways results in induction of type I interferons (IFNs), while activation of TLR2-and TLR5-mediated pathways do not. However, activation of TLR7, TLR8 and TLR9 signaling pathways also leads to induction of Type I IFNs, although this occurs through mechanisms distinct from TLR3/4-mediated induction.

[000234] Once engaged, TLRs initiate a signal transduction cascade leading to activation of NFκB via the adapter protein myeloid differentiation primary response gene 88 (MyD88) and recruitment of the IL-1 receptor associated kinase (IRAK). The MyD88-dependent pathway is analogous to signaling by the IL-1 receptors, and it is regarded that MyD88, harboring a C-terminal TIR domain and an N-terminal death domain, associates with the TIR domain of TLRs. Upon stimulation, MyD88 recruits IRAK-4 to TLRs through interaction of the death domains of both molecules, and facilitates IRAK-4-mediated phosphorylation of IRAK-1. Phosphorylation of IRAK-1 then leads to recruitment of TNF-receptor associated factor 6 (TRAF6), leading to the activation of two distinct signaling pathways. One pathway leads to activation of AP-1 transcription factors through activation of MAP kinases. Another pathway activates the TAK1/TAB complex, which enhances activity of the IκB kinase (IKK) complex. Once activated, the IKK complex induces phosphorylation and subsequent degradation of the NFκB inhibitor IκB, which leads to nuclear translocation of transcription factor NFκB and the initiation of transcription of genes whose promoters contain NFκB binding sites, such as cytokines. The MyD88-dependent pathway plays a crucial role and is essential for inflammatory cytokine production through all TLRs.

[000235] Stimulation of TLR8-expressing cells, such as PBMCs results in production of high levels of IL-12, IFN-γ, IL-1, TNF-α, IL-6 and other inflammatory cytokines. Similarly, stimulation of TLR7-expressing cells, such as plasmacytoid dendritic cells, results in production of high levels of interferon-α (IFNα) and low levels of inflammatory cytokines. Thus, through activation of dendritic cells and other antigen-presenting cells, TLR7, TLR8 or TLR9 engagement

and cytokine production is expected to activate diverse innate and acquired immune response mechanisms leading to the destruction of pathogens, infected cells or tumor cells.

[000236] Compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are useful as modulators of toll-like receptor activity, and are used in the treatment of a wide variety of diseases and/or disorders associated with such receptors. In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are modulators of TLR7 activity and are useful in the treatment of diseases and/or disorders associated with TLR7. In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are agonists of TLR7 activity and are useful in the treatment of diseases and/or disorders associated with TLR7. In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are modulators of TLR8 activity and are useful in the treatment of diseases and/or disorders associated with TLR8. In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are agonists of TLR8 activity and are useful in the treatment of diseases and/or disorders associated with TLR8.

[000237] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of respiratory diseases and/or disorders including, but not limited to, asthma, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, exercise-induced asthma, drug-induced asthma (including aspirin and NSAID-induced) and dust-induced asthma, chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute

and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus.

[000238] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of dermatological disorders including, but not limited to, psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, basal cell carcinoma, actinic keratosis, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis;cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions.

[000239] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of ocular diseases and/or disorders including, but not limited to, blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune, degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial.

[000240] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of genitourinary diseases and/or disorders including, but not limited to, nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female).

[000241] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or

combinations provided herein are used in the treatment of allograft rejection including, but not limited to, acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease.

[000242] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of other auto-immune and allergic disorders including, but not limited to, rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, Crohns disease, inflammatory bowel disease (IBD), Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome and Sazary syndrome.

[000243] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are used in the treatment of cancer including, but not limited to, prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumor recurrences, and paraneoplastic syndromes. In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are useful as modulators of toll-like receptor activity, and are used in the treatment of neoplasias including, but not limited to, basal cell carcinoma, squamous cell carcinoma, actinic keratosis, melanoma, carcinomas, sarcomas, leukemias, renal cell carcinoma, Kaposi's sarcoma, myelogeous leukemia, chronic lymphocytic leukemia and multiple myeloma.

[000244] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of infectious diseases including, but not limited to, viral diseases such as genital warts, common warts, plantar warts, respiratory syncytial virus (RSV), hepatitis B, hepatitis C, Dengue virus, herpes simplex virus (by way of example only, HSV-I, HSV-II, CMV, or VZV), molluscum contagiosum, vaccinia, variola, lentivirus, human immunodeficiency virus (HIV), human papilloma virus (HPV), cytomegalovirus (CMV), varicella zoster virus (VZV), rhinovirus, enterovirus, adenovirus, coronavirus (e.g., SARS), influenza, para-

influenza, mumps virus, measles virus, papovavirus, hepadnavirus, flavivirus, retrovirus, arenavirus (by way of example only, LCM, Junin virus, Machupo virus, Guanarito virus and Lassa Fever) and filovirus (by way of example only, ebola virus or marbug virus).

[000245] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of bacterial, fungal, and protozoal infections including, but not limited to, tuberculosis and mycobacterium avium, leprosy; pneumocystis carnii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection, leishmaniasis, infections caused by bacteria of the genus *Escherichia, Enterobacter, Salmonella, Staphylococcus, Klebsiella, Proteus, Pseudomonas, Streptococcus, and Chlamydia*, and fungal infections such as *candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis.*

[000246] In certain embodiments, the compounds of Formula (I) and (I-A), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, are used as immune potentiators. In certain embodiments, the compounds provided herein are included in immunogenic compositions or are used in combination with immunogenic compositions. In certain embodiments, the immunogenic compositions are useful as vaccines, and the compound is present in an amount sufficient to enhance an immune response to the vaccine, or to an antigen admixed with the compound. The vaccine comprises at least one antigen, which may be an bacterial antigen or a cancer-associated antigen, or a viral antigen. In certain embodiments, the compounds of Formula (I) or (I-A), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are included in therapeutic vaccines or are used in combination with therapeutic vaccines. In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are included in prophylactic vaccines or used in combination with prophylactic vaccines. In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are included in, or are used in combination with, therapeutic viral vaccines. In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are included in, or are used in combination with, with cancer vaccines.

[000247] In other embodiments, the compounds of Formula (I), or a pharmaceutically acceptable

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 September 2009 (11.09.2009)

PCT

(10) International Publication Number
WO 2009/111337 A1

(51) International Patent Classification:
C07D 221/12 (2006.01) *C07D 491/12* (2006.01)
C07D 471/04 (2006.01) *C07D 495/04* (2006.01)
C07D 471/12 (2006.01) *A61K 31/4375* (2006.01)
C07D 491/056 (2006.01) *A61P 37/04* (2006.01)

(21) International Application Number:
PCT/US2009/035563

(22) International Filing Date:
27 February 2009 (27.02.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/033,139 3 March 2008 (03.03.2008) US
61/148,336 29 January 2009 (29.01.2009) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR,

[Continued on next page]

(54) Title: COMPOUNDS AND COMPOSITIONS AS TLR ACTIVITY MODULATORS

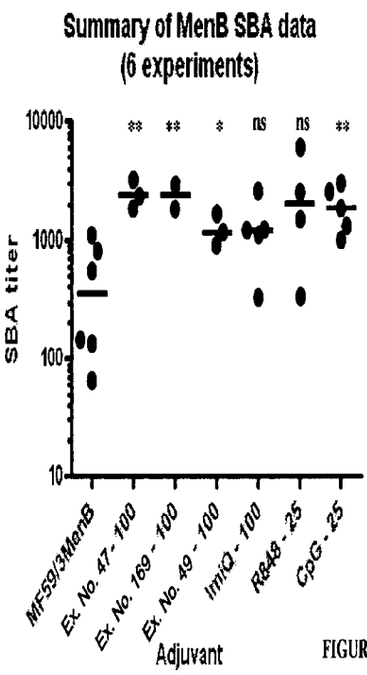
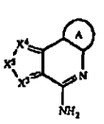


FIGURE 5



(I)

(57) Abstract: The invention provides a novel class of compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with Toll-Like Receptors, including TLR7 and TLR8. In one aspect, the compounds are useful as adjuvants for enhancing the effectiveness of a vaccine (formula I) wherein: X^3 is N; X^4 is N Or CR^3; X^5 is $-CR^4=CR^5$.

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KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, 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, ST, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, 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 (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

COMPOUNDS AND COMPOSITIONS AS TLR ACTIVITY MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority under 35 U.S.C. §119(e) to U.S. Provisional Patent Application No. 61/033,139, filed March 3, 2008 and U.S. Provisional Patent Application No. 61/148,336, filed January 29, 2009. The disclosure of the priority applications are incorporated herein by reference in their entirety and for all purposes.

STATEMENT OF GOVERNMENT SUPPORT

[0002] This invention was made in part with Government support under DTRA Grant No. HDTRA1-07-9-0001 awarded by the Department of Defense. The Government has certain rights in the invention.

FIELD OF THE INVENTION

[0003] The invention relates to modulators of Toll-Like Receptors (TLRs), and methods of using such compounds.

BACKGROUND OF THE INVENTION

[0004] Early detection of specific classes of pathogens is accomplished by the innate immune system with the help of pattern recognition receptors (PRRs). The detected pathogens include viruses, bacteria, protozoa and fungi, and each constitutively expresses a set of class-specific, mutation-resistant molecules called pathogen-associated molecular patterns (PAMPs). These molecular markers may be composed of proteins, carbohydrates, lipids, nucleic acids or combinations thereof, and may be located internally or externally. Examples of PAMPs include bacterial carbohydrates (lipopolysaccharide or LPS, mannose), nucleic acids (bacterial or viral DNA or RNA), peptidoglycans and lipotechoic acids (from Gram positive bacteria), *N*-formylmethionine, lipoproteins and fungal glucans.

[0005] Pattern recognition receptors have evolved to take advantage of three PAMP qualities. First, constitutive expression allows the host to detect the pathogen regardless of its life cycle stage. Second, the PAMPs are class specific, which allows the host to distinguish between pathogens and thereby tailor its response. Third, mutation resistance allows the host to recognize the pathogen regardless of its particular strain.

[0006] Pattern recognition receptors are involved in more than just recognition of pathogens via their PAMPs. Once bound, pattern recognition receptors tend to cluster, recruit other extracellular and intracellular proteins to the complex, and initiate signaling cascades that

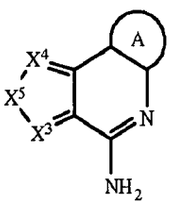
ultimately impact transcription. Additionally, pattern recognition receptors are involved in activation of complement, coagulation, phagocytosis, inflammation, and apoptosis functions in response to pathogen detection.

[0007] Pattern recognition receptors (PRRs) may be divided into endocytic PRRs or signaling PRRs. The signaling PRRs include the large families of membrane-bound Toll-like receptors (TLRs) and cytoplasmic NOD-like receptors, while the endocytic PRRs promote the attachment, engulfment and destruction of microorganisms by phagocytes without relaying an intracellular signal, are found on all phagocytes and mediate removal of apoptotic cells. In addition, endocytic PRRs recognize carbohydrates and include mannose receptors of macrophages, glucan receptors present on all phagocytes and scavenger receptors that recognize charged ligands.

SUMMARY OF THE INVENTION

[0008] Provided herein are compounds and pharmaceutical compositions thereof, which are useful modulators of toll-like receptors.

[0009] In one aspect provided herein such compounds, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, having a structure according to Formula (I) as described herein. Certain embodiments of the invention include compounds of Formula (I-A), methods of using them, and pharmaceutical compositions comprising these compounds:



Formula (I-A)

wherein:

X^3 is N; X^4 is N or CR^3, and X^5 is $-CR^4=CR^5-$;

R^1 and R^2 are H; R^3 is H;

R^4 and R^5 are each independently selected from H, halogen, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-SR^7$, $-(CH_2)_nOR^7$, $-(CH_2)_nR^7$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, $-C_1$-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-

C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, -NO_2, -R^7, -OR^8, -$C(O)R^8$, -$OC(O)R^8$, -$C(O)OR^8$, -$N(R^9)_2$, -$P(O)(OR^8)_2$, -$OP(O)(OR^8)_2$, -$P(O)(OR^{10})_2$, -$OP(O)(OR^{10})_2$, -$C(O)N(R^9)_2$, –$S(O)_2R^8$, –$S(O)_2N(R^9)_2$, and -$NR^9S(O)_2R^8$; or R^3 and R^4, or R^4 and R^5, when present on adjacent ring atoms, can optionally be linked together to form a 5-6 membered ring, wherein the 5-6 membered ring is optionally substituted with R^7;

each L is independently selected from a bond, -$(O(CH_2)_m)_t$-, C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene, wherein the C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene of L are each optionally substituted with 1 to 4 substituents independently selected from halogen, -R^8, -OR^8, -$N(R^9)_2$, -$P(O)(OR^8)_2$, -$OP(O)(OR^8)_2$, -$P(O)(OR^{10})_2$, and -$OP(O)(OR^{10})_2$;

R^7 is selected from H, C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, and C_3-C_8heterocycloalkyl groups of R^7 are each optionally substituted with 1 to 3 R^{13} groups, and each R^{13} is independently selected from halogen, –CN, -LR^9, -LOR^9, -OLR^9, -LR^{10}, -LOR^{10}, -OLR^{10}, -LR^8, -LOR^8, -OLR^8, -LSR^8, -LSR^{10}, -$LC(O)R^8$, -$OLC(O)R^8$, -$LC(O)OR^8$, -$LC(O)R^{10}$, -$LOC(O)OR^8$, -$LC(O)NR^9R^{11}$, -$LC(O)NR^9R^8$, -$LN(R^9)_2$, -LNR^9R^8, -LNR^9R^{10}, -$LC(O)N(R^9)_2$, –$LS(O)_2R^8$, -$LS(O)R^8$, -$LC(O)NR^8OH$, -$LNR^9C(O)R^8$, -$LNR^9C(O)OR^8$, –$LS(O)_2N(R^9)_2$, -$OLS(O)_2N(R^9)_2$, -$LNR^9S(O)_2R^8$, -$LC(O)NR^9LN(R^9)_2$, -$LP(O)(OR^8)_2$, -$LOP(O)(OR^8)_2$, -$LP(O)(OR^{10})_2$ and -$OLP(O)(OR^{10})$;

each R^8 is independently selected from H, -$CH(R^{10})_2$, C_1-C_8alkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, C_1-C_6hydroxyalkyl and C_1-C_6haloalkoxy, wherein the C_1-C_8alkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, C_1-C_6hydroxyalkyl and C_1-C_6haloalkoxy groups of R^8 are each optionally substituted with 1 to 3 substituents independently selected from –CN, R^{11}, -OR^{11}, -SR^{11}, -$C(O)R^{11}$, -$OC(O)R^{11}$, -$C(O)N(R^9)_2$, -$C(O)OR^{11}$, -$NR^9C(O)R^{11}$, -NR^9R^{10}, -$NR^{11}R^{12}$, -$N(R^9)_2$, -OR^9, -OR^{10}, -$C(O)NR^{11}R^{12}$, -$C(O)NR^{11}OH$, –$S(O)_2R^{11}$, –$S(O)R^{11}$, –$S(O)_2NR^{11}R^{12}$, -$NR^{11}S(O)_2R^{11}$, -$P(O)(OR^{11})_2$, and -$OP(O)(OR^{11})_2$;

each R^9 is independently selected from H, -$C(O)R^8$, -$C(O)OR^8$, -$C(O)R^{10}$, -$C(O)OR^{10}$, -$S(O)_2R^{10}$, -C_1-C_6 alkyl, C_1-C_6 heteroalkyl and C_3-C_6 cycloalkyl, or each R^9 is independently a C_1-C_6alkyl that together with N they are attached to form a C_3-C_8heterocycloalkyl, wherein the C_3-

C_8heterocycloalkyl ring optionally contains an additional heteroatom selected from N, O and S, and wherein the C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, or C_3-C_8heterocycloalkyl groups of R^9 are each optionally substituted with 1 to 3 substituents independently selected from –CN, R^{11}, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-OC(O)R^{11}$, $-C(O)OR^{11}$, $-NR^{11}R^{12}$, $-C(O)NR^{11}R^{12}$, $-C(O)NR^{11}OH$, $-S(O)_2R^{11}$, $-S(O)R^{11}$, $-S(O)_2NR^{11}R^{12}$, $-NR^{11}S(O)_2R^{11}$, $-P(O)(OR^{11})_2$, and $-OP(O)(OR^{11})_2$;

each R^{10} is independently selected from aryl, C_3-C_8cycloalkyl, C_3-C_8heterocycloalkyl or a heteroaryl, wherein the aryl, C_3-C_8cycloalkyl, C_3-C_8heterocycloalkyl or heteroaryl groups are optionally substituted with 1 to 3 substituents selected from halogen, $-R^8$, $-OR^8$, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9CO_2R^8$, $-CO_2R^8$, $-C(O)R^8$ and $-C(O)N(R^9)_2$;

R^{11} and R^{12} are independently selected from H, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl groups of R^{11} and R^{12} are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, R^8, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-NR^8C(O)R^8$, $-NR^8C(O)OR^8$, $-C(O)N(R^9)_2$, C_3-C_8heterocycloalkyl, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, $-NR^9S(O)_2R^8$, C_1-C_6haloalkyl and C_1-C_6haloalkoxy, and wherein the aryl and heteroaryl groups of R^{11} and R^{12} are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, R^8, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-C(O)N(R^9)_2$, C_3-C_8heterocycloalkyl, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, $-NR^9S(O)_2R^8$, C_1-C_6haloalkyl and C_1-C_6haloalkoxy; or R^{11} and R^{12} are each independently C_1-C_6alkyl and taken together with the N atom to which they are attached form an optionally substituted C_3-C_8heterocycloalkyl ring optionally containing an additional heteroatom selected from N, O and S;

Ring A is an aryl or a heteroaryl, wherein the aryl and heteroaryl groups of Ring A are optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$; or two adjacent R^A substituents on Ring A form a 5-6 membered ring that contains up to two heteroatoms as ring members; n is, independently at each occurrence, 0, 1, 2, 3, 4, 5, 6, 7 or 8; each m is independently selected from 1, 2, 3, 4, 5 and 6, andt is 1, 2, 3, 4, 5, 6, 7 or 8.

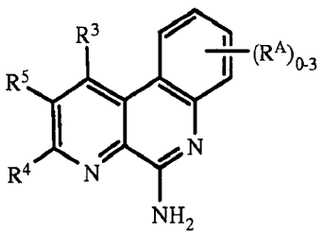
[00010] In certain embodiments of such compounds of Formulas (I) or (I-A), one of R^4 and R^5 is H; and the other of R^4 and R^5 is selected from halogen, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, $-SR^7$, $-(CH_2)_nOR^7$, $-(CH_2)_nR^7$, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, $-R^7$, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-C(O)N(R^9)_2$, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, and $-NR^9S(O)_2R^8$.

[00011] In certain embodiments of such compounds of Formulas (I) or (I-A), Ring A is phenyl, naphthyl, fluorenyl, indenyl, azulenyl or anthracenyl, each of which is optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$. In certain embodiments of such compounds of Formulas (I) or (I-A), Ring A is phenyl or naphthyl.

[00012] In certain embodiments of the such compounds of Formulas (I) or (I-A), Ring A is benzofuranyl, benzofurazanyl, benzoxazolyl, benzopyranyl, benzthiazolyl, benzothienyl, benzazepinyl, benzimidazolyl, benzothiopyranyl, benzo[1,3]dioxole, benzo[b]furyl, benzo[b]thienyl, cinnolinyl, furazanyl, furyl, furopyridinyl, imidazolyl, indolyl, indolizinyl, indolin-2-one, indazolyl, isoindolyl, isoquinolinyl, isoxazolyl, isothiazolyl, 1,8-naphthyridinyl, oxazolyl, oxaindolyl, oxadiazolyl, pyrazolyl, pyrrolyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinoxalinyl, quinolinyl, quinazolinyl, 4H-quinolizinyl, thiazolyl, thiadiazolyl, thienyl, triazinyl,triazolyl or tetrazolyl, each of which is optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-$

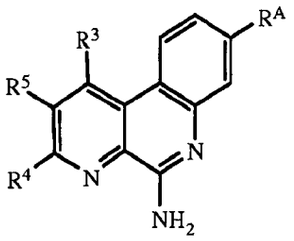
$C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$. In certain embodiments of such compounds of Formulas (I) or (I-A), Ring A is pyridyl, benzo[1,3]dioxole, thienyl, benzothienyl, benzofuranyl, or indolyl.

[00013] In certain embodiments of compounds of Formulas (I) and Formula (I-A), the compounds have a structure of Formula (X-A):



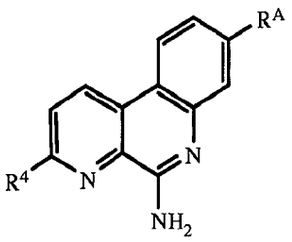
Formula (X-A).

[00014] In certain embodiments of compounds of Formulas (I) or Formula (I-A), the compounds have a structure of Formula (XI):

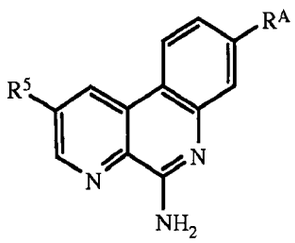


Formula (XI).

[00015] In certain embodiments of compounds of Formulas (I) or Formula (I-A), the compound have a structure of Formula (XII) or Formula (XIII):



Formula (XII)

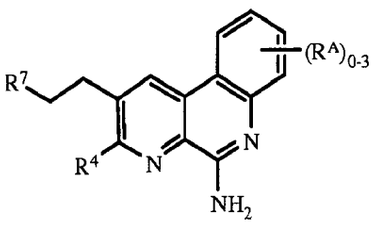


Formula (XIII).

[00016] In certain embodiments of such compounds of Formulas (I) or (I-A), Formulas (X-A) and (XI) to (XIII), R^4 and R^5 are independently selected from H, halogen, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, $-SR^7$, $-(CH_2)_nR^7$, $-(CH_2)_nOR^7$, $-C_1$-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy, wherein the

C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, -R^7, -OR^8, -$C(O)R^8$, -$OC(O)R^8$, -$C(O)OR^8$, -$N(R^9)_2$, -$P(O)(OR^8)_2$, -$OP(O)(OR^8)_2$, -$P(O)(OR^{10})_2$, -$OP(O)(OR^{10})_2$, -$C(O)N(R^9)_2$, –$S(O)_2R^8$, –$S(O)_2N(R^9)_2$, and -$NHS(O)_2R^8$. In other embodiments of such compounds of Formulas (I) or (I-A), Formulas (X-A) and (XI) to (XIII), R^4 and R^5 are independently selected from H, halogen, -$C(O)OR^7$, -$C(O)R^7$, -$C(O)N(R^{11}R^{12})$, -$N(R^{11}R^{12})$, -$N(R^9)_2$, -$NHN(R^9)_2$, -LR^8, -LR^{10}, -OLR^8, -OLR^{10}, -SR^7, -$(CH_2)_nOR^7$, -$(CH_2)_nR^7$, -C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy, wherein the -C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy groups are each optionally substituted with R^7.

[00017] In certain embodiments of compounds of Formulas (I) and Formula (I-A), the compounds have a structure of Formula (XIV):



Formula (XIV).

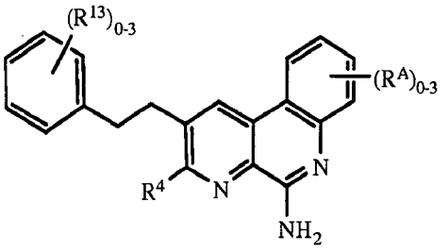
[00018] In certain embodiments of such compounds of Formulas (XIV) R^4 is selected from H, halogen, -$C(O)OR^7$, -$C(O)R^7$, -$C(O)N(R^{11}R^{12})$, -$N(R^{11}R^{12})$, -SR^7, -$(CH_2)_nR^7$, -$(CH_2)_nOR^7$, -C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy, wherein the C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, -R^7, -OR^8, -$C(O)R^8$, -$OC(O)R^8$, -$C(O)OR^8$, -$N(R^9)_2$, -$P(O)(OR^8)_2$, -$OP(O)(OR^8)_2$, -$P(O)(OR^{10})_2$, -$OP(O)(OR^{10})_2$, -$C(O)N(R^9)_2$, –$S(O)_2R^8$, –$S(O)_2N(R^9)_2$, and -$NHS(O)_2R^8$. In other embodiments of such compounds of Formulas (XIV), R^4 is selected from H, halogen, -$C(O)OR^7$, -$C(O)R^7$, -$C(O)N(R^{11}R^{12})$, -$N(R^{11}R^{12})$, -SR^7, -$(CH_2)_nOR^7$, -$(CH_2)_nR^7$, -C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy, wherein the -C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy groups are each optionally substituted with R^7.

[00019] In certain embodiments of such compounds of Formulas (I) or (I-A), Formulas (X-A) and (XI) to (XIV), R^7 is selected from H, C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl and C_3-C_8heterocycloalkyl groups of R^7 are each optionally substituted with 1 to 3 R^{13} groups and each R^{13} is independently selected from halogen, –CN, -LR^9, -LOR^9, -OLR^9, -LR^{10}, -LOR^{10}, -OLR^{10}, -LR^8,

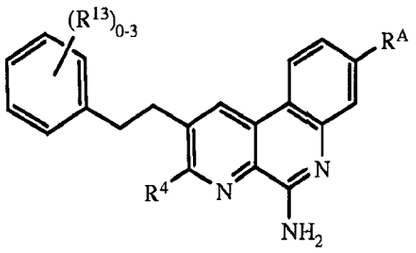
-LOR^8, -OLR^8, -LSR^8, -LSR^{10}, -$LC(O)R^8$, -$OLC(O)R^8$, -$LC(O)OR^8$, -$LC(O)R^{10}$, -$LOC(O)OR^8$, -$LC(O)NR^9R^{11}$, -$LC(O)NR^9R^8$, -$LN(R^9)_2$, -LNR^9R^8, -LNR^9R^{10}, -$LC(O)N(R^9)_2$, -$LS(O)_2R^8$, -$LS(O)R^8$, -$LC(O)NR^8OH$, -$LNR^9C(O)R^8$, -$LNR^9C(O)OR^8$, -$LS(O)_2N(R^9)_2$, -$OLS(O)_2N(R^9)_2$, -$LNR^9S(O)_2R^8$, -$LC(O)NR^9LN(R^9)_2$, -$LP(O)(OR^8)_2$, -$LOP(O)(OR^8)_2$, -$LP(O)(OR^{10})_2$ and -$OLP(O)(OR^{10})_2$.

[00020] In certain embodiments of such compounds of Formulas (I) or (I-A), Formulas (X-A) and (XI) to (XIV), R^7 is selected from H, C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl groups are each optionally substituted with 1-3 R^{13} groups and each R^{13} is independently selected from halogen, C_1-C_6haloalkyl, LR^8, LR^9, -LOR^8 and -OLR^8.

[00021] In certain embodiments of compounds of Formulas (I) or (I-A), Formulas (X-A) and (XI) to (XIV), have a structure of Formula (XV) or Formula (XVI):



Formula (XV)



Formula (XVI).

[00022] In certain embodiments of such compounds of Formulas (I) or (I-A), Formulas (X-A) and (XI) to (XVI), R^{13} is selected from -LR^9, -LOR^9, -OLR^9, -LR^{10}, -LOR^{10}, -OLR^{10}, -LR^8, -LOR^8, -OLR^8, -LSR^8, -LSR^{10}, -$LC(O)R^8$, -$OLC(O)R^8$, -$LC(O)OR^8$, -$LC(O)R^{10}$, -$LOC(O)OR^8$, -$LC(O)NR^9R^{11}$, -$LC(O)NR^9R^8$, -$LN(R^9)_2$, -LNR^9R^8, -LNR^9R^{10}, -$LC(O)N(R^9)_2$, -$LS(O)_2R^8$, -$LS(O)R^8$, -$LC(O)NR^8OH$, -$LNR^9C(O)R^8$, -$LNR^9C(O)OR^8$, -$LS(O)_2N(R^9)_2$, -$OLS(O)_2N(R^9)_2$, -$LNR^9S(O)_2R^8$, -$LC(O)NR^9LN(R^9)_2$, -$LP(O)(OR^8)_2$, -$LOP(O)(OR^8)_2$, -$LP(O)(OR^{10})_2$ and -$OLP(O)(OR^{10})_2$.

[00023] In certain embodiments of such compounds of Formulas (I) or (I-A), Formulas (X-A) and (XI) to (XVI), R^{10} is an aryl or a heteroaryl, wherein the aryl and heteroaryl groups are optionally substituted with 1 to 3 substituents selected from halogen, $-R^8$, -OR^8, and -$N(R^9)_2$.

[00024] In certain embodiments of such compounds of Formulas (I) or (I-A) Formulas (X-A) and (XI) to (XVI), R^{10} is phenyl optionally substituted with 1 to 3 substituents selected from halogen, $-R^8$, -OR^8, and -$N(R^9)_2$.

[00025] In certain embodiments of such compounds of Formulas (I) or (I-A), Formulas (X-

A) and (XI) to (XVI), R^8 is selected from H, C_1-C_6alkyl and C_1-C_6haloalkyl. In certain embodiments of the compounds of Formula XIII, XIV, XV or XVI, the compound is selected from: 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 2-(4-(dimethylamino)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine, and 2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine. Each of these compounds individually comprises a preferred embodiment of the compounds, compositions, and methods described herein.

[00026] In certain embodiments of the compounds, compositions and methods described herein, the compound of Formulas (I) is selected from 2-methylbenzo[f][1,7]naphthyridin-5-amine; 2-propylbenzo[f][1,7]naphthyridin-5-amine; 2-ethylbenzo[f][1,7]naphthyridin-5-amine; 2-(3-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-difluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; methyl 5-aminobenzo[f][1,7]naphthyridine-3-carboxylate; 5-amino-N-methylbenzo[f][1,7]naphthyridine-3-carboxamide; (5-aminobenzo[f][1,7]naphthyridin-3-yl)methanol; 8-phenylbenzo[f][1,7]naphthyridin-5-amine; 3-(ethoxymethyl)benzo[f][1,7]naphthyridin-5-amine; benzo[f][1,7]naphthyridine-3,5-diamine; benzo[f][1,7]naphthyridin-5-amine; methyl 5-aminobenzo[f][1,7]naphthyridine-8-carboxylate; 5-aminobenzo[f][1,7]naphthyridine-8-carboxylic acid; ethyl 5-aminobenzo[f][1,7]naphthyridine-8-carboxylate; (5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol; 5-aminobenzo[f][1,7]naphthyridine-3-carboxylic acid; 5-aminobenzo[f][1,7]naphthyridine-3-carbaldehyde; 2-(2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-chlorobenzo[f][1,7]naphthyridin-5-amine; ethyl 5-aminobenzo[f][1,7]naphthyridine-9-carboxylate; 8-methoxybenzo[f][1,7]naphthyridin-5-amine; 8-(methylsulfonyl)benzo[f][1,7]naphthyridin-5-amine; 8-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine; 8-fluorobenzo[f][1,7]naphthyridin-5-amine; 3-methoxybenzo[f][1,7]naphthyridin-5-amine; 3-butoxybenzo[f][1,7]naphthyridin-5-amine; 3-

(benzyloxy)benzo[f][1,7]naphthyridin-5-amine; 3-methylbenzo[f][1,7]naphthyridin-5-amine; 3-chlorobenzo[f][1,7]naphthyridin-5-amine; N3,N3-dimethylbenzo[f][1,7]naphthyridine-3,5-diamine; N3-butylbenzo[f][1,7]naphthyridine-3,5-diamine; 3-vinylbenzo[f][1,7]naphthyridin-5-amine; 3-ethylbenzo[f][1,7]naphthyridin-5-amine; 3-fluorobenzo[f][1,7]naphthyridin-5-amine; 2-phenethylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(naphthalen-1-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(naphthalen-2-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoic acid; 3-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoic acid; 2-(3-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (3-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol; 2-(4-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-butylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-butylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-propylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,5-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-propylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2,4,5-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,5-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-isopropylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-heptylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-isobutoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-((2-methoxyethoxy)methoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-phenoxyethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(tert-butyldimethylsilyloxy)ethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-phenylbutoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(allyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(3-phenylpropoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(heptan-4-yloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-methylpent-3-enyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-cyclohexylethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-isopropoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(3,3-dimethylbutoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(tert-butyldimethylsilyloxy)ethoxy)-2-

methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide; N-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide; N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-4-methylbenzenesulfonamide; 3-methyl-9-p-tolyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzonitrile; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-aminoethyl)-3-methylbenzamide; 8-methyl-2-(2-methyl-4-(1H-tetrazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; methyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoate; methyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetic acid; 6-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)hexan-1-ol; 7-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)heptanoic acid; 11-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)undecan-1-ol; ethyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)acetate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)acetic acid; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propanoic acid; 6-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)hexanoic acid; 8-methyl-2-(2-methyl-4-(methylthio)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(methylsulfonyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(hexyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-phenethoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(pentyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-methylpentyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(thiophen-3-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; (5-aminobenzo[f][1,7]naphthyridin-2-yl)methanol; 2-(3,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3,4-dimethylphenethyl)-8-

methylbenzo[f][1,7]naphthyridin-5-amine; 2-(3,5-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(benzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-nitroethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(aminomethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; N2,8-dimethylbenzo[f][1,7]naphthyridine-2,5-diamine; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-phenylethanol; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(4-methoxyphenyl)ethanol; 2-(biphenyl-2-yl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,6-dimethylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(5-methoxypyridin-2-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoic acid; 5-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-4-methylpyridin-2(1H)-one; 6-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)pyridin-3-ol; 8-methyl-2-(4-(trifluoromethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,3-dihydro-1H-inden-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,3-dihydro-1H-inden-5-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; (E)-3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylic acid; (E)-ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylate; 8-(prop-1-en-2-yl)benzo[f][1,7]naphthyridin-5-amine; 5-aminobenzo[f][1,7]naphthyridine-8-carbonitrile; (E)-8-(3-methylbut-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-methylprop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; (E)-8-(pent-1-enyl)benzo[f][1,7]naphthyridin-5-amine; (E)-8-styrylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-(2-cyclopropylvinyl)-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; 8-pentylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-(2-cyclopropylvinyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; 9-phenethylpyrido[1,2-c][1,7]naphthyridin-6-amine; methyl 5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridine-8-carboxylate; 8-nitrobenzo[f][1,7]naphthyridin-5-amine; 3-chloro-8-methylbenzo[f][1,7]naphthyridin-5-amine; methyl 5-amino-3-chlorobenzo[f][1,7]naphthyridine-8-carboxylate; methyl 5-amino-3-fluorobenzo[f][1,7]naphthyridine-8-carboxylate; 3-chloro-8-nitrobenzo[f][1,7]naphthyridin-5-amine; (5-amino-3-chlorobenzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-phenethylbenzo[f][1,7]naphthyridin-8-yl)methanol; 4-(2-(5-amino-8-fluorobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzaldehyde; 2-(4-(2-(5-amino-8-fluorobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzylamino)ethanol; 3-(4-(2-(5-amino-8-

fluorobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzylamino)propan-1-ol; 8-fluoro-2-(4-((2-methoxyethylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 3-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol; 2-(2-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-ethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-ethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(piperidin-1-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-tert-butylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(piperidin-1-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(3,5-dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-hydroxybenzimidamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzonitrile; 8-methyl-2-(4-(1-morpholinoethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-aminophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)guanidine; 8-methyl-2-(4-(1-(phenethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetonitrile; 2-(4-(piperidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzyl)piperidin-4-ol; 2-(4-(aminomethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-((ethylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-aminopropan-2-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-(1-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid; 8-methyl-2-(4-(1-(phenylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-ethyl-8-methylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)methanol; 8-methyl-2-propylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(1H-indol-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-ethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-phenoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-

dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol; 2-(2-(2,3-dihydrobenzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethanol; 3-methyl-9-phenyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine; 8-methylbenzo[f][1,7]naphthyridine-2,5-diamine; 1-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)propan-2-ol; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetonitrile; N-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetamide; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(2,4-dimethylphenyl)ethanol; 2-(2-(6-methoxy-4-methylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)butan-1-ol; methyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoate; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-1-ol; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-2-methylbutan-2-ol; 2-(4-(aminomethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (E)-ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylate; ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzyl)propane-1,3-diol; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoic acid; 5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridine-8-carbaldehyde; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoate; 8-methyl-2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-2-ol; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoic acid; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)methanol; 8-methyl-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 8-methyl-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; (E)-3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylic acid; ethyl 3-(5-amino-2-(4-methoxy-2-

methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoate; 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoic acid; 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propan-1-ol; 5-aminobenzo[f][1,7]naphthyridin-8-ol; 5-aminobenzo[f][1,7]naphthyridine-8-carbaldehyde; 1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanol; 1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanone; 8-isopropylbenzo[f][1,7]naphthyridin-5-amine; 8-vinylbenzo[f][1,7]naphthyridin-5-amine; 8-ethylbenzo[f][1,7]naphthyridin-5-amine; 8-(methoxymethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; benzo[f][1,7]naphthyridine-5,8-diamine; 8-(aminomethyl)benzo[f][1,7]naphthyridin-5-amine; 3-fluoro-8-methylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-3-fluorobenzo[f][1,7]naphthyridin-8-yl)methanol; 3-chlorobenzo[f][1,7]naphthyridine-5,8-diamine; 3-fluorobenzo[f][1,7]naphthyridine-5,8-diamine; 8-isobutylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-(prop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 8-propylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)benzo[f][1,7]naphthyridin-5-amine; 8-phenethylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(4-bromophenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 2-(4-methoxy-2-methylphenethyl)-8-pentylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; (2-(2-(1H-indol-5-yl)ethyl)-5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol; methyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,3-dimethylbenzamide; N-(2-acetamidoethyl)-4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide; 2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,N,3-trimethylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-hydroxyethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-3-methylbenzamide; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-

methylphenyl)(pyrrolidin-1-yl)methanone; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(diethylamino)ethyl)-3-methylbenzamide; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(4-ethylpiperazin-1-yl)methanone; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(piperazin-1-yl)methanone; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methyl-N-(2-(pyrrolidin-1-yl)ethyl)benzamide; 4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N-methylbenzamide; 2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 2-(4-butoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(biphenyl-4-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-((1,3-dihydroisobenzofuran-1-yl)methyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-methylallyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(isopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl propyl carbonate; ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoate; 2-(4-(cyclopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(cyclobutylmethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-1-phenylethanone; 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)ethanol; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-N,N-dimethylacetamide; 8-methyl-2-(2-methyl-4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethanol; diethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonate; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonic acid; 2-(4-butoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol; 2-(2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethanol; ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoate; 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol; 4-(2-(5-amino-8-

methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl ethyl carbonate; methyl 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoate; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoic acid; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)butanoic acid; 2-(4-(isopentyloxy)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl hexyl carbonate; 2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; diethyl 3-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)propylphosphonate; diethyl 3-(2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethoxy)propylphosphonate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl dimethylsulfamate; (5-amino-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 2-(4-(dimethylamino)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone; 2-(4-((dimethylamino)methyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(1-(dimethylamino)ethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone oxime; 8-methyl-2-(4-((methylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzylamino)ethanol; 8-methyl-2-(4-(pyrrolidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3,4-dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)ethanol; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanol; 8-methyl-2-(4-(oxazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propanenitrile; (2R)-2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propan-1-ol; 8-methyl-2-(4-(1-(piperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; ((2S)-1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidin-2-yl)methanol; N1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N2,N2-dimethylethane-1,2-diamine; 3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-

yl)ethyl)phenyl)ethylamino)propanoic acid; 8-methyl-2-(4-(1-(4-methylpiperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; N2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N1,N1-dimethylpropane-1,2-diamine; 8-methyl-2-(4-(1-(2-(pyridin-4-yl)ethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; N1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N2,N2-diethylethane-1,2-diamine; 2-(4-(dimethylamino)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid; 4-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)phenol; 1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2 yl)ethyl)phenyl)ethyl)pyrrolidin-3-ol, and 2-(4-(2-aminopropan-2-yl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine.

[00027] In certain embodiments of the compounds, compositions and methods described herein, the compound of Formulas (I-A) is selected from the following compounds and their pharmaceutically acceptable salts:

2-methylbenzo[f][1,7]naphthyridin-5-amine; 2-propylbenzo[f][1,7]naphthyridin-5-amine; 2-ethylbenzo[f][1,7]naphthyridin-5-amine; 2-(3-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; methyl 5-aminobenzo[f][1,7]naphthyridine-3-carboxylate; (5-aminobenzo[f][1,7]naphthyridin-3-yl)methanol; benzo[f][1,7]naphthyridin-5-amine; (5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol; 2-(2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-chlorobenzo[f][1,7]naphthyridin-5-amine; ethyl 5-aminobenzo[f][1,7]naphthyridine-9-carboxylate; 8-methoxybenzo[f][1,7]naphthyridin-5-amine; 8-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine; 8-fluorobenzo[f][1,7]naphthyridin-5-amine; 3-methylbenzo[f][1,7]naphthyridin-5-amine; 3-fluorobenzo[f][1,7]naphthyridin-5-amine; 2-phenethylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(naphthalen-1-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(naphthalen-2-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoic acid; 3-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoic acid; 2-(3-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (3-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol; 2-(4-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-

butylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-butylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-propylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,5-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-propylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2,4,5-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,5-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-isopropylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-heptylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-isobutoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-((2-methoxyethoxy)methoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-phenoxyethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-phenylbutoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(allyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(3-phenylpropoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(heptan-4-yloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-methylpent-3-enyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-cyclohexylethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-isopropoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(3,3-dimethylbutoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide; N-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide; N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-4-methylbenzenesulfonamide; 3-methyl-9-p-tolyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzonitrile; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-aminoethyl)-3-methylbenzamide; 8-methyl-2-(2-methyl-4-(1H-tetrazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; methyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoate; methyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoic

acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetic acid; 6-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)hexan-1-ol; 7-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)heptanoic acid; 11-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)undecan-1-ol; ethyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)acetate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)acetic acid; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propanoic acid; 6-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)hexanoic acid; 8-methyl-2-(2-methyl-4-(methylthio)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(methylsulfonyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(hexyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-phenethoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(pentyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-methylpentyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(thiophen-3-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; (5-aminobenzo[f][1,7]naphthyridin-2-yl)methanol; 2-(3,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3,4-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(3,5-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(benzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-nitroethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(aminomethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; N^2,8-dimethylbenzo[f][1,7]naphthyridine-2,5-diamine; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-phenylethanol; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(4-methoxyphenyl)ethanol; 2-(biphenyl-2-yl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,6-dimethylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(5-methoxypyridin-2-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoic acid; 5-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-4-methylpyridin-2(1H)-one; 6-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)pyridin-3-ol; 8-methyl-2-(4-(trifluoromethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,3-dihydro-1H-inden-5-

yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,3-dihydro-1H-inden-5-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; (E)-3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylic acid; (E)-ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylate; (E)-8-(2-cyclopropylvinyl)-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; 8-pentylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-(2-cyclopropylvinyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-2-phenethylbenzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 3-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol; 2-(2-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-ethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-ethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(piperidin-1-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-tert-butylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(piperidin-1-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(3,5-dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-hydroxybenzimidamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzonitrile; 8-methyl-2-(4-(1-morpholinoethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-aminophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)guanidine; 8-methyl-2-(4-(1-(phenethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetonitrile; 2-(4-(piperidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzyl)piperidin-4-ol; 2-(4-(aminomethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-((ethylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-aminopropan-2-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-(1-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid; 8-methyl-2-(4-(1-(phenylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-ethyl-8-

methylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)methanol; 8-methyl-2-propylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(1H-indol-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-ethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-phenoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol; 2-(2-(2,3-dihydrobenzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethanol; 3-methyl-9-phenyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine; 8-methylbenzo[f][1,7]naphthyridine-2,5-diamine; 1-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)propan-2-ol; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetonitrile; N-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetamide; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(2,4-dimethylphenyl)ethanol; 2-(2-(6-methoxy-4-methylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)butan-1-ol; methyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoate; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-1-ol; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-2-methylbutan-2-ol; 2-(4-(aminomethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (E)-ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylate; ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzyl)propane-1,3-diol; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoic acid; 5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridine-8-carbaldehyde; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoate; 8-methyl-2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-2-ol; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoic acid; (4-(2-(5-amino-8-

methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)methanol; 8-methyl-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 8-methyl-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; (E)-3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylic acid; ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoate; 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoic acid; 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propan-1-ol; 5-aminobenzo[f][1,7]naphthyridin-8-ol; 5-aminobenzo[f][1,7]naphthyridine-8-carbaldehyde; 1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanol; 1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanone; 8-isopropylbenzo[f][1,7]naphthyridin-5-amine; 8-vinylbenzo[f][1,7]naphthyridin-5-amine; 8-ethylbenzo[f][1,7]naphthyridin-5-amine; 8-(methoxymethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; benzo[f][1,7]naphthyridine-5,8-diamine; 8-(aminomethyl)benzo[f][1,7]naphthyridin-5-amine; 3-fluoro-8-methylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-3-fluorobenzo[f][1,7]naphthyridin-8-yl)methanol; 3-chlorobenzo[f][1,7]naphthyridine-5,8-diamine; 3-fluorobenzo[f][1,7]naphthyridine-5,8-diamine; 8-isobutylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-(prop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 8-propylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)benzo[f][1,7]naphthyridin-5-amine; 8-phenethylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(4-bromophenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 2-(4-methoxy-2-methylphenethyl)-8-pentylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; (2-(2-(1H-indol-5-yl)ethyl)-5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol; methyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,3-dimethylbenzamide; N-(2-acetamidoethyl)-4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide; 2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide; 4-(2-(5-amino-8-

methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,N,3-trimethylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-hydroxyethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-3-methylbenzamide; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(pyrrolidin-1-yl)methanone; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(diethylamino)ethyl)-3-methylbenzamide; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(4-ethylpiperazin-1-yl)methanone; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(piperazin-1-yl)methanone; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methyl-N-(2-(pyrrolidin-1-yl)ethyl)benzamide; 4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N-methylbenzamide; 2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 2-(4-butoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(biphenyl-4-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-((1,3-dihydroisobenzofuran-1-yl)methyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-methylallyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(isopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl propyl carbonate; ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoate; 2-(4-(cyclopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(cyclobutylmethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-1-phenylethanone; 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)ethanol; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-N,N-dimethylacetamide; 8-methyl-2-(2-methyl-4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethanol; diethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonate; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonic acid; 2-(4-butoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol; 2-(2-(4-(2-(5-

aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethanol; ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoate; 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl ethyl carbonate; methyl 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoate; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoic acid; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)butanoic acid; 2-(4-(isopentyloxy)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl hexyl carbonate; 2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; diethyl 3-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)propylphosphonate; diethyl 3-(2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethoxy)propylphosphonate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl dimethylsulfamate; (5-amino-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 2-(4-(dimethylamino)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone; 2-(4-((dimethylamino)methyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(1-(dimethylamino)ethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone oxime; 8-methyl-2-(4-((methylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzylamino)ethanol; 8-methyl-2-(4-(pyrrolidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3,4-dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)ethanol; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanol; 8-methyl-2-(4-(oxazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propanenitrile; (2R)-2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propan-1-ol; 8-methyl-2-(4-(1-

(piperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; ((2S)-1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidin-2-yl)methanol; N^1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^2,N^2-dimethylethane-1,2-diamine; 3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propanoic acid; 8-methyl-2-(4-(1-(4-methylpiperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; N^2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^1,N^1-dimethylpropane-1,2-diamine; 8-methyl-2-(4-(1-(2-(pyridin-4-yl)ethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; N^1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^2,N^2-diethylethane-1,2-diamine; 2-(4-(dimethylamino)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid; 4-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)phenol; 1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2 yl)ethyl)phenyl)ethyl)pyrrolidin-3-ol; and 2-(4-(2-aminopropan-2-yl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine.

[00028] In certain embodiments of compounds of Formula (XVI), or a pharmaceutically acceptable salt thereof, each R^4, R^A and R^{13} is independently selected from H, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH_2OH$, $-OCH_3$, $-COOCH_3$, F, Cl, Br, $-CH_2OCH_3$, $-COOCH_2CH_3$, , $CH_2OCH_2CH_3$, $-N(CH_3)_2$, $-((O(CH_2)_2)_{2\text{-}4}OH$, $-O(CH_2)_{2\text{-}4}$-OH, $-O(CH_2)_{2\text{-}4}$-(PO_3H_2), $-O(CH_2)_{2\text{-}4}$-COOH, $-O(CH_2)_{2\text{-}4}$-$CH(CH_3)_2$, C_2-C_6 alkyl substituted with 1-3 substituents selected from –OH, $-CH_3$, cyclopropyl, $-O(CH_2)_{2\text{-}4}$-COOH, $-O(CH_2)_{2\text{-}4}(PO_3H_2)$, -COOH, $COOCH_3$, and $-COOCH_2CH_3$. In other embodiments of compounds of Formula (XVI), R^4 is H. In other embodiments such compounds of Formula (XVI), have one to three R^{13} groups. In other embodiments of such compounds of Formula (XVI), R^A is H or Me. In other embodiments such compounds of Formula (XVI), have two R^{13} groups selected from the group consisting of $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH_2OH$, $-OCH_3$, $-COOCH_3$, $-COOCH_2CH_3$, F, Cl, Br, $-CH_2OCH_3$, $CH_2OCH_2CH_3$, $-N(CH_3)_2$, $-((O(CH_2)_2)_{2\text{-}4}OH$, $-O(CH_2)_{2\text{-}4}$-OH, $-O(CH_2)_{2\text{-}4}$-(PO_3H_2), $-O(CH_2)_{2\text{-}4}$-COOH, $-O(CH_2)_{2\text{-}4}$-$CH(CH_3)_2$, C_2-C_6 alkyl substituted with 1-3 substituents selected from –OH, $-CH_3$, cyclopropyl, $-O(CH_2)_{2\text{-}4}$-COOH, $-O(CH_2)_{2\text{-}4}(PO_3H_2)$, -COOH, $COOCH_3$, and $-COOCH_2CH_3$. In other embodiments such compounds of Formula (XVI) are selected from: 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2,4-

dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 2-(4-(dimethylamino)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine, and 2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine.

[00029] Another aspect provided herein are pharmaceutical compositions that include a therapeutically effective amount of a compound of Formula (I) described above and a pharmaceutically acceptable carrier.

[00030] In certain embodiments of this aspect, the pharmaceutical composition is formulated for intravenous administration, intravitrial administration, intramuscular administration, oral administration, rectal administration inhalation, nasal administration, topical administration, ophthalmic administration or otic administration. In other embodiments, the pharmaceutical compositions are in the form of a tablet, a pill, a capsule, a liquid, an inhalant, a nasal spray solution, a suppository, a solution, an emulsion, an ointment, eye drop or ear drop. In other embodiments, such pharmaceutical compositions further include one or more additional therapeutic agents.

[00031] Another aspect provided herein are medicaments for treating a disease or disorder in a patient where modulation of a TLR receptor is implicated and such medicaments include a therapeutically effective amount of a compound of Formula (I). In certain embodiments of such medicaments, the TLR receptor is TLR7. In other embodiments of such medicaments, the TLR receptor is TLR8. In certain embodiments of such medicaments, the compound is a TLR receptor agonist. In certain embodiments of such medicaments, the compound is a TLR7 receptor agonist. In certain embodiments of such medicaments, the compound is a TLR8 receptor agonist.

[00032] Another aspect provided herein is the use of a compound of Formula (I) in the manufacture of a medicament for treating a disease or disorder in a patient where modulation of a TLR receptor is implicated.

[00033] Another aspect provided herein includes methods for modulating a TLR receptor, wherein the method include administering to a system or a subject in need thereof, a therapeutically effective amount of a compound of Formula (I), or pharmaceutically acceptable salts or pharmaceutical compositions thereof, thereby modulating the TLR receptor. In certain embodiments of such methods, the TLR receptor is TLR7. In other embodiments of such methods, the TLR receptor is TLR8. In certain embodiments of such methods, the compound is a TLR receptor agonist. In certain embodiments of such methods, the compound is a TLR7 receptor

agonist. In certain embodiments of such methods, the compound is a TLR8 receptor agonist. In certain embodiments of such methods, the methods include administering the compound to a cell or tissue system or to a human or animal subject.

[00034] In certain embodiments of the methods provided herein for the treatment of a subject for a specified condition or disorder where a TLR is implicated, such methods further comprise an optional step of identifying a subject in need of such treatment.

[00035] Another aspect provided herein includes methods for treating a disease or disorder where modulation of TLR receptor is implicated, wherein the method includes administering to a system or subject in need of such treatment an effective amount of a compound of Formula (I), or pharmaceutically acceptable salts or pharmaceutical compositions thereof, thereby treating the disease or disorder. In certain embodiments of such methods, the TLR receptor is TLR7. In other embodiments of such methods, the TLR receptor is TLR8. In certain embodiments of such methods, the compound is a TLR receptor agonist. In certain embodiments of such methods, the compound is a TLR7 receptor agonist. In certain embodiments of such methods, the compound is a TLR8 receptor agonist. In certain embodiments of such methods, the methods include administering the compound to a cell or tissue system or to a human or animal subject.

[00036] In certain embodiments of such methods, the disease or condition is an infectious disease, an inflammatory disease, a respiratory disease, a dermatological disease or an autoimmune disease. In certain embodiments of such methods, the disease or condition is asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohns disease, bronchitis, dermatitis, actinic keratosis, basal cell carcinoma, allergic rhinitis, psoriasis, scleroderma, urticaria, rheumatoid arthritis, multiple sclerosis, cancer, breast cancer, HIV or lupus.

[00037] Another aspect provided herein includes methods for treating a cell-proliferative disease, comprising administering to a system or subject in need of such treatment an effective amount of a compound of Formula (I), or pharmaceutically acceptable salts or pharmaceutical compositions thereof; wherein the cell-proliferative disease is lymphoma, osteosarcoma, melanoma, or a tumor of breast, renal, prostate, colorectal, thyroid, ovarian, pancreatic, neuronal, lung, uterine or gastrointestinal tumor.

[00038] Another aspect provided herein are pharmaceutical composition that include a compound of Formula (I) of (I-A), an antigen and a pharmaceutically acceptable carrier, wherein such pharmaceutical compositions are immunogenic compositions, and the compound is an

immune potentiator and is present in an amount effective to enhance an immune response to the antigen, in a subject receiving the composition. In certain embodiments, such pharmaceutical compositions, further includes one or more immunoregulatory agents. In certain embodiments, the one or more immunoregulatory agents include one or more adjuvants. In certain embodiments, such adjuvants are selected from adjuvants that are a mineral-containing composition, an oil emulsion, a saponin formulation, a virosome, a virus-like particle, a bacterial derivative, a microbial derivative, a human immunomodulator, a bioadhesive, a mucoadhesive, a microparticle, a liposome, a polyoxyethylene ether formulation, a polyoxyethylene ester formulation, a polyphosphazene, a muramyl peptide, or an imidazoquinolone compound. In certain embodiments, the adjuvant is an oil emulsion. In certain embodiments the immunogenic compositions are useful as vaccines, and the compound is present in an amount sufficient to produce an immunostimulatory effect upon administration.

[00039] Another aspect provided herein includes methods for enhancing the effectiveness of an immunogenic composition, comprising adding an effective amount of a compound Formula (I) or (I-A) to the immunogenic composition.

[00040] Another aspect provided herein are immunogenic compositions comprising a compound of Formula (I-A), and an antigen, wherein the amount of the compound is an amount effective to enhance an immune response to the antigen in a subject to whom the composition is administered. In certain embodiments of such immunogenic compositions the antigen is a bacterial antigen. In certain embodiments of such immunogenic compositions the bacterial antigen is an antigen of a strain of *Neisseria meningitides*. In other embodiments of such immunogenic compositions the antigen is a viral antigen or a fungal antigen. In other embodiments such immunogenic compositions further comprising an additional adjuvant. In certain embodiments of such immunogenic compositions the antigen is a polypeptide. In certain embodiments of such immunogenic compositions the polypeptide has at least 85% identity to a sequence selected from the group consisting of SEQ ID NOs: 1-6 provided herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[00041] FIG. 1 shows the serum bactericidal antibody ("SBA") titer of certain compounds disclosed herein to enhance the immune response to a bacterial antigen. The dose of the compound in μg is indicated on the left, and the fold-change over the response elicited with MF59/3MenB is shown to the right of each bar.The results are compared to "CpG" (CpG oligonucleotide), R848, and Immiquimod (ImiQ).

[00042] FIG. 2 shows the serum bactericidal antibody ("SBA") titer of compound 47 disclosed herein to enhance the immune response to a bacterial antigen. The dose of the compound in μg is indicated on the left, and the fold-change over the response elicited with MF59/3MenB is shown to the right of each bar.The results are compared to "CpG" (CpG oligonucleotide), R848, and Immiquimod (ImiQ).

[00043] FIG. 3 shows the serum bactericidal antibody ("SBA") titer of compound 47 disclosed herein to enhance the immune response to a bacterial antigen. The dose of the compound in μg is indicated on the left, and the fold-change over the response elicited with MF59/3MenB is shown to the right of each bar.The results are compared to "CpG" (CpG oligonucleotide), R848, and Immiquimod (ImiQ).

[00044] FIG. 4 shows the serum bactericidal antibody ("SBA") titer of compound 169 disclosed herein to enhance the immune response to a bacterial antigen. The dose of the compound in μg is indicated on the left, and the fold-change over the response elicited with MF59/3MenB is shown to the right of each bar.The results are compared to "CpG" (CpG oligonucleotide), R848, and Immiquimod (ImiQ).

[00045] FIG. 5 is a compilation of the data shown in Figures 1-4.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[00046] The term "alkenyl," as used herein, refers to a partially unsaturated branched or straight chain hydrocarbon having at least one carbon-carbon double bond. Atoms oriented about the double bond are in either the cis (Z) or trans (E) conformation. An alkenyl group can be optionally substituted. As used herein, the terms "C_2-C_3alkenyl", "C_2-C_4alkenyl", "C_2-C_5alkenyl", "C_2-C_6alkenyl", "C_2-C_7alkenyl", and "C_2-C_8alkenyl" refer to an alkenyl group containing at least 2, and at most 3, 4, 5, 6, 7 or 8 carbon atoms, respectively. If not otherwise specified, an alkenyl group generally is a C_2-C_6 alkenyl. Non-limiting examples of alkenyl groups, as used herein, include ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl and the like.

[00047] The term "alkenylene," as used herein, refers to a partially unsaturated branched or straight chain divalent hydrocarbon radical derived from an alkenyl group. An alkenylene group can be optionally substituted. As used herein, the terms "C_2-C_3alkenylene", "C_2-C_4alkenylene", "C_2-C_5alkenylene", "C_2-C_6alkenylene", "C_2-C_7alkenylene", and "C_2-C_8alkenylene" refer to an alkenylene group containing at least 2, and at most 3, 4, 5, 6, 7 or 8 carbon atoms respectively. If not otherwise specified, an alkenylene group generally is a C_1-C_6 alkenylene.Non-limiting

examples of alkenylene groups as used herein include, ethenylene, propenylene, butenylene, pentenylene, hexenylene, heptenylene, octenylene, nonenylene, decenylene and the like.

[00048] The term "alkyl," as used herein, refers to a saturated branched or straight chain hydrocarbon. An alkyl group can be optionally substituted. As used herein, the terms "C_1-C_3alkyl", "C_1-C_4alkyl", "C_1-C_5alkyl", "C_1-C_6alkyl", "C_1-C_7alkyl" and "C_1-C_8alkyl" refer to an alkyl group containing at least 1, and at most 3, 4, 5, 6, 7 or 8 carbon atoms, respectively. If not otherwise specified, an alkyl group generally is a C_1-C_6 alkyl. Non-limiting examples of alkyl groups as used herein include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, hexyl, heptyl, octyl, nonyl, decyl and the like.

[00049] The term "alkylene," as used herein, refers to a saturated branched or straight chain divalent hydrocarbon radical derived from an alkyl group. An alkylene group can be optionally substituted. As used herein, the terms "C_1-C_3alkylene", "C_1-C_4alkylene", "C_1-C_5alkylene", "C_1-C_6alkylene", "C_1-C_7alkylene" and "C_1-C_8alkylene" refer to an alkylene group containing at least 1, and at most 3, 4, 5, 6, 7 or 8 carbon atoms respectively. If not otherwise specified, an alkylene group generally is a C_1-C_6 alkylene. Non-limiting examples of alkylene groups as used herein include, methylene, ethylene, n-propylene, isopropylene, n-butylene, isobutylene, sec-butylene, t-butylene, n-pentylene, isopentylene, hexylene and the like.

[00050] The term "alkynyl," as used herein, refers to a partially unsaturated branched or straight chain hydrocarbon having at least one carbon-carbon triple bond. An alkynyl group can be optionally substituted. As used herein, the terms "C_2-C_3alkynyl", "C_2-C_4alkynyl", "C_2-C_5alkynyl", "C_2-C_6alkynyl", "C_2-C_7alkynyl", and "C_2-C_8alkynyl" refer to an alkynyl group containing at least 2, and at most 3, 4, 5, 6, 7 or 8 carbon atoms, respectively. If not otherwise specified, an alkynyl group generally is a C_2-C_6 alkynyl. Non-limiting examples of alkynyl groups, as used herein, include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl and the like.

[00051] The term "alkynylene," as used herein, refers to a partially unsaturated branched or straight chain divalent hydrocarbon radical derived from an alkynyl group. An alkynylene group can be optionally substituted. As used herein, the terms "C_2-C_3alkynylene", "C_2-C_4alkynylene", "C_2-C_5alkynylene", "C_2-C_6alkynylene", "C_2-C_7alkynylene", and "C_2-C_8alkynylene" refer to an alkynylene group containing at least 2, and at most 3, 4, 5, 6, 7 or 8 carbon atoms respectively. If not otherwise specified, an alkynylene group generally is a C_2-C_6 alkynylene. Non-limiting examples of alkynylene groups as used herein include, ethynylene, propynylene, butynylene, pentynylene, hexynylene, heptynylene, octynylene, nonynylene, decynylene and the like.

[00052] The term "alkoxy," as used herein, refers to the group $-OR_a$, where R_a is an alkyl group as defined herein. An alkoxy group can be optionally substituted. As used herein, the terms "C_1-C_3alkoxy", "C_1-C_4alkoxy", "C_1-C_5alkoxy", "C_1-C_6alkoxy", "C_1-C_7alkoxy" and "C_1-C_8alkoxy" refer to an alkoxy group wherein the alkyl moiety contains at least 1, and at most 3, 4, 5, 6, 7 or 8, carbon atoms. Non-limiting examples of alkoxy groups, as used herein, include methoxy, ethoxy, n-propoxy, isopropoxy, n-butyloxy, t-butyloxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, decyloxy and the like.

[00053] The term "aryl," as used herein, refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. An aryl group can be optionally substituted. Non-limiting examples of aryl groups, as used herein, include phenyl, naphthyl, fluorenyl, indenyl, azulenyl, anthracenyl and the like.

[00054] The term "arylene," as used means a divalent radical derived from an aryl group. An arylene group can be optionally substituted.

[00055] The term "cyano," as used herein, refers to a -CN group.

[00056] The term "cycloalkyl," as used herein, refers to a saturated or partially unsaturated, monocyclic, fused bicyclic, fused tricyclic or bridged polycyclic ring assembly. As used herein, the terms "C_3-C_5 cycloalkyl", "C_3-C_6 cycloalkyl", "C_3-C_7 cycloalkyl", "C_3-C_8 cycloalkyl, "C_3-C_9 cycloalkyl and "C_3-C_{10} cycloalkyl refer to a cycloalkyl group wherein the saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly contain at least 3, and at most 5, 6, 7, 8, 9 or 10, carbon atoms. A cycloalkyl group can be optionally substituted. Non-limiting examples of cycloalkyl groups, as used herein, include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclopentenyl, cyclohexenyl, decahydronaphthalenyl, 2,3,4,5,6,7-hexahydro-1H-indenyl and the like.

[00057] The term "halogen," as used herein, refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I).

[00058] The term "halo," as used herein, refers to the halogen radicals: fluoro (-F), chloro (-Cl), bromo (-Br), and iodo (-I).

[00059] The terms "haloalkyl" or "halo-substituted alkyl," as used herein, refers to an alkyl group as defined herein, substituted with one or more halogen groups, wherein the halogen groups are the same or different. A haloalkyl group can be optionally substituted. Non-limiting examples of such branched or straight chained haloalkyl groups, as used herein, include methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl substituted with one or more halogen groups, wherein the

halogen groups are the same or different, including, but not limited to, trifluoromethyl, pentafluoroethyl, and the like.

[00060] The terms "haloalkenyl" or "halo-substituted alkenyl," as used herein, refers to an alkenyl group as defined herein, substituted with one or more halogen groups, wherein the halogen groups are the same or different. A haloalkenyl group can be optionally substituted. Non-limiting examples of such branched or straight chained haloalkenyl groups, as used herein, include ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl and the like substituted with one or more halogen groups, wherein the halogen groups are the same or different.

[00061] The terms "haloalkynyl" or "halo-substituted alkynyl," as used herein, refers to an alkynyl group as defined above, substituted with one or more halogen groups, wherein the halogen groups are the same or different. A haloalkynyl group can be optionally substituted. Non-limiting examples of such branched or straight chained haloalkynyl groups, as used herein, include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, and the like substituted with one or more halogen groups, wherein the halogen groups are the same or different.

[00062] The term "haloalkoxy," as used herein, refers to an alkoxy group as defined herein, substituted with one or more halogen groups, wherein the halogen groups are the same or different. A haloalkoxy group can be optionally substituted. Non-limiting examples of such branched or straight chained haloalkynyl groups, as used herein, include methoxy, ethoxy, n-propoxy, isopropoxy, n-butyloxy, t-butyloxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, decyloxy and the like, substituted with one or more halogen groups, wherein the halogen groups are the same or different.

[00063] The term "heteroalkyl," as used herein, refers to an alkyl group as defined herein wherein one or more carbon atoms are independently replaced by one or more of oxygen, sulfur, nitrogen, or combinations thereof.

[00064] The term "heteroaryl," as used herein, refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms selected from nitrogen, oxygen and sulfur, and wherein each ring in the system contains 3 to 7 ring members. A heteroaryl group may contain one or more substituents. A heteroaryl group can be optionally substituted. Non-limiting examples of heteroaryl groups, as used herein, include benzofuranyl, benzofurazanyl, benzoxazolyl, benzopyranyl, benzthiazolyl, benzothienyl, benzazepinyl, benzimidazolyl, benzothiopyranyl, benzo[1,3]dioxole, benzo[b]furyl, benzo[b]thienyl, cinnolinyl, furazanyl, furyl, furopyridinyl, imidazolyl, indolyl, indolizinyl, indolin-2-one, indazolyl,

isoindolyl, isoquinolinyl, isoxazolyl, isothiazolyl, 1,8-naphthyridinyl, oxazolyl, oxaindolyl, oxadiazolyl, pyrazolyl, pyrrolyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinoxalinyl, quinolinyl, quinazolinyl, 4H-quinolizinyl, thiazolyl, thiadiazolyl, thienyl, triazinyl,triazolyl and tetrazolyl.

[00065] The term "heterocycloalkyl," as used herein, refers to a cycloalkyl, as defined herein, wherein one or more of the ring carbons are replaced by a moiety selected from -O-, -N=, -NR-, -C(O)-, -S-, -S(O) - or -S(O)2-, wherein R is hydrogen, C_1-C_4alkyl or a nitrogen protecting group, with the proviso that the ring of said group does not contain two adjacent O or S atoms. A heterocycloalkyl group can be optionally substituted. Non-limiting examples of heterocycloalkyl groups, as used herein, include morpholino, pyrrolidinyl, pyrrolidinyl-2-one, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, 2H-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, 1,3-dioxolanyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, 1,4-dioxanyl, 1,4-dithianyl, thiomorpholinyl, azepanyl, hexahydro-1,4-diazepinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, thioxanyl, azetidinyl, oxetanyl, thietanyl, oxepanyl, thiepanyl, 1,2,3,6-tetrahydropyridinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, and 3-azabicyclo[4.1.0]heptanyl.

[00066] The term "heteroatom," as used herein, refers to one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon.

[00067] The term "hydroxyl," as used herein, refers to the group -OH.

[00068] The term "hydroxyalkyl," as used herein refers to an alkyl group as defined herein substituted with one or more hydroxyl group. Non-limiting examples of branched or straight chained "C_1-C_6 hydroxyalkyl groups as used herein include methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl groups substituted with one or more hydroxyl groups.

[00069] The term "isocyanato," as used herein, refers to a –N=C=O group.

[00070] The term "isothiocyanato," as used herein, refers to a –N=C=S group.

[00071] The term "mercaptyl," as used herein, refers to an (alkyl)S- group.

[00072] The term "optionally substituted," as used herein, means that the referenced group may or may not be substituted with one or more additional group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, hydroxyl, alkoxy, mercaptyl, cyano, halo, carbonyl, thiocarbonyl, isocyanato, thiocyanato, isothiocyanato, nitro, perhaloalkyl, perfluoroalkyl, and amino, including mono- and di-substituted amino groups,

and the protected derivatives thereof. Non-limiting examples of optional substituents include, halo, –CN, =O, =N-OH, =N-OR, =N-R, –OR, -C(O)R, -C(O)OR, -OC(O)R, -OC(O)OR, -C(O)NHR, -$C(O)NR_2$, -OC(O)NHR, -$OC(O)NR_2$, -SR-, -S(O)R, -$S(O)_2R$, -NHR, -$N(R)_2$, -NHC(O)R, –NRC(O)R, -NHC(O)OR, -NRC(O)OR, $S(O)_2NHR$, –$S(O)_2N(R)_2$, -$NHS(O)_2NR_2$, -$NRS(O)_2NR_2$, -$NHS(O)_2R$, -$NRS(O)_2R$, C_1-C_8alkyl, C_1-C_8alkoxy, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, halo-substituted C_1-C_8alkyl, and halo-substituted C_1-C_8alkoxy, where each R is independently selected from H, halo, C_1-C_8alkyl, C_1-C_8alkoxy, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, halo-substituted C_1-C_8alkyl, and halo-substituted C_1-C_8alkoxy. The placement and number of such substituent groups is done in accordance with the well-understood valence limitations of each group, for example =O is a suitable substituent for an alkyl group but not for an aryl group.

[00073] The term "solvate," as used herein, refers to a complex of variable stoichiometry formed by a solute (by way of example, a compound of Formula (I), or a salt thereof, as described herein) and a solvent. Non-limiting examples of a solvent are water, acetone, methanol, ethanol and acetic acid.

[00074] The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[00075] The term "administration" or "administering" of the subject compound means providing a compound of Formula (I), a pharmaceutically acceptable salt, a pharmaceutically acceptable solvate, or prodrug thereof to a subject in need of treatment.

[00076] The term "cancer," as used herein refers to an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread). The types of cancer include, but is not limited to, solid tumors (such as those of the bladder, bowel, brain, breast, endometrium, heart, kidney, lung, lymphatic tissue (lymphoma), ovary, pancreas or other endocrine organ (thyroid), prostate, skin (melanoma) or hematological tumors (such as the leukemias).

[00077] The term "carrier," as used herein, refers to chemical compounds or agents that facilitate the incorporation of a compound described herein into cells or tissues.

[00078] The terms "co-administration" or "combined administration" or the like as used herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

[00079] The term "dermatological disorder," as used herein refers to a skin disorder. Such

dermatological disorders include, but are not limited to, proliferative or inflammatory disorders of the skin such as, atopic dermatitis, bullous disorders, collagenoses, contact dermatitis eczema, Kawasaki Disease, rosacea, Sjogren-Larsso Syndrome, actinic keratosis, basal cell carcinoma and urticaria.

[00080] The term "diluent," as used herein, refers to chemical compounds that are used to dilute a compound described herein prior to delivery. Diluents can also be used to stabilize compounds described herein.

[00081] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of a compound described herein being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study.

[00082] The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[00083] The terms "fibrosis" or "fibrosing disorder," as used herein, refers to conditions that follow acute or chronic inflammation and are associated with the abnormal accumulation of cells and/or collagen and include but are not limited to fibrosis of individual organs or tissues such as the heart, kidney, joints, lung, or skin, and includes such disorders as idiopathic pulmonary fibrosis and cryptogenic fibrosing alveolitis.

[00084] The term "iatrogenic," as used herein, means a condition, disorder, or disease created or worsened by medical or surgical therapy.

[00085] The term "immunologically effective amount," as used herein, means that the administration of a sufficient amount to an individual, either in a single dose or as part of a series, that is effective for treatment or prevention of an immunological disease or disorder. This amount varies depending upon the health and physical condition of the individual to be treated, age, the taxonomic group of individual to be treated (e.g. non-human primate, primate, etc.), the capacity

of the individual's immune system to synthesize antibodies, the degree of protection desired, the formulation of the vaccine, the treating doctor's assessment of the medical situation, and other relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials.

[00086] The term "inflammatory disorders," as used herein, refers to those diseases or conditions that are characterized by one or more of the signs of pain (dolor, from the generation of noxious substances and the stimulation of nerves), heat (calor, from vasodilatation), redness (rubor, from vasodilatation and increased blood flow), swelling (tumor, from excessive inflow or restricted outflow of fluid), and loss of function (functio laesa, which may be partial or complete, temporary or permanent). Inflammation takes many forms and includes, but is not limited to, inflammation that is one or more of the following: acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing, seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative. Inflammatory disorders further include, without being limited to those affecting the blood vessels (polyarteritis, temporal arthritis); joints (arthritis: crystalline, osteo-, psoriatic, reactive, rheumatoid, Reiter's); gastrointestinal tract (Disease,); skin (dermatitis); or multiple organs and tissues (systemic lupus erythematosus).

[00087] The term "modulate," as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[00088] The term "modulator," as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an agonist or an antagonist.

[00089] The terms "ocular disease" or "ophthalmic disease," as used herein, refer to diseases which affect the eye or eyes and potentially the surrounding tissues as well. Ocular or ophthalmic diseases include, but are not limited to, conjunctivitis, retinitis, scleritis, uveitis, allergic conjuctivitis, vernal conjunctivitis, papillary conjunctivitis and cytomegalovirus (CMV) retinitis.

[00090] The term "pharmaceutically acceptable," as used herein, refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compounds described herein. Such materials are administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the

composition in which it is contained.

[00091] The term "pharmaceutically acceptable salt," as used herein, refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compounds described herein.

[00092] The terms "combination" or "pharmaceutical combination," as used herein mean a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, by way of example, a compound of Formula (I) and an additional therapeutic agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, by way of example, a compound of Formula (I) and an additional therapeutic agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

[00093] The terms "composition" or "pharmaceutical composition," as used herein, refers to a mixture of at least one compound, such as the compounds of Formula (I) described herein, with at least one and optionally more than one other pharmaceutically acceptable chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients.

[00094] The term "prodrug," as used herein, refers to an agent that is converted into the parent drug *in vivo*. A non-limiting example of a prodrug of the compounds described herein is a compound described herein administered as an ester which is then metabolically hydrolyzed to a carboxylic acid, the active entity, once inside the cell. A further example of a prodrug is a short peptide bonded to an acid group where the peptide is metabolized to reveal the active moiety.

[00095] The term "respiratory disease," as used herein, refers to diseases affecting the organs that are involved in breathing, such as the nose, throat, larynx, trachea, bronchi, and lungs. Respiratory diseases include, but are not limited to, asthma, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, seasonal allergic rhinitis, perennial allergic rhinitis, chronic obstructive pulmonary disease, including

chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis, and hypoxia.

[00096] The term "subject" or "patient," as used herein, encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, humans, chimpanzees, apes monkeys, cattle, horses, sheep, goats, swine; rabbits, dogs, cats, rats, mice, guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like. Frequently the subject is a human, and may be a human who has been diagnosed as in need of treatment for a disease or disorder disclosed herein.

[00097] The term "TLR modulator," as used herein, refers to a compound which modulates a TLR receptor.

[00098] The term "TLR disease" or a "disease or disorder associated with TLR activity," as used herein, refers to any disease state associated with a toll-like receptor. Such diseases or disorders include, but are not limited to, infectious diseases, inflammatory diseases, respiratory diseases and autoimmune diseases, such as, by way of example only, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDs), Crohns disease, bronchitis, dermatitis, allergic rhinitis, psoriasis, scleroderma, urticaria, rheumatoid arthritis, multiple sclerosis, cancer, HIV and lupus.

[00099] The term "therapeutically effective amount," as used herein, refers to any amount of a compound which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

[000100] The terms "treat," "treating" or "treatment," as used herein, refers to methods of alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

[000101] Other objects, features and advantages of the methods, compositions and combinations described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only.

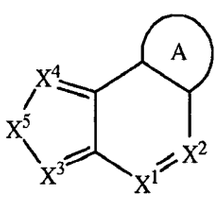
Description of the Preferred Embodiments

[000102] Provided herein are compounds and pharmaceutical compositions thereof, which are modulators of toll-like receptors (TLRs). In certain embodiments, certain compounds described herein, and pharmaceutical compositions thereof, are agonists of toll-like receptors. In other embodiments, such compounds and pharmaceutical compositions thereof, are agonists of TLR7. In other embodiments, such compounds and pharmaceutical compositions thereof, are agonists of TLR8. In other embodiments, such compounds and pharmaceutical compositions thereof, are agonists of both TLR7 and TLR8, that is such compounds and pharmaceutical compositions thereof, are dual agonists of TLR7 and TLR8.

[000103] Provided herein are compounds, pharmaceutical compositions and methods for the treatment and/or prevention of diseases and/or disorders associated with TLR activity. In certain embodiments, such TLRs are TLR7 and TLR8.

[000104] The TLR modulators provided herein include compounds having the structure of Formula (I), and pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof:

[000105] Provided herein are compounds, pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, having the structure of Formula (I):



Formula (I)

wherein:

X^1 is N or $CN(R^1R^2)$; X^2 is N or $CN(R^1R^2)$, provided that when X^1 is $CN(R^1R^2)$ then X^2 is N;

X^3 is N or CR^6;

X^4 is N or CR^3; and X^5 is $-CR^4=CR^5-$, $-CR^4=N-$ or $-N=CR^5-$;

R^1 and R^2 are each independently selected from H, $-C(O)R^8$, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl,

wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_3-C_8cycloalkyl, or C_3-C_8heterocycloalkyl groups of R^1 and R^2 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, =O, C_1-C_6 alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_3-C_8cycloalkyl, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-C(O)N(R^9)_2$, C_3-C_8heterocycloalkyl, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, $-N\ R^9S(O)_2R^8$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$, $-OLP(O)(OR^{10})_2$, C_1-C_6haloalkyl and C_1-C_6haloalkoxy, and

wherein the aryl and heteroaryl groups of R^1 and R^2 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, C_1-C_6 alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_3-C_8cycloalkyl, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-C(O)N(R^9)_2$, C_3-C_8heterocycloalkyl, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, $-NR^9S(O)_2R^8$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$, $-OLP(O)(OR^{10})_2$, C_1-C_6haloalkyl and C_1-C_6haloalkoxy,

or R^1 and R^2 are each independently C_1-C_6alkyl that can be substituted as described above and, taken together with the N atom to which they are attached, form an optionally substituted C_3-C_8heterocycloalkyl;

R^3 and R^6 are each independently selected from H, halogen, C_1-C_6alkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl,

wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, or C_3-C_8heterocycloalkyl groups of R^3 and R^6 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, =O, R^7, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-C(O)N(R^9)_2$, $-S(O)_2R^8$, $-S(O)_2\ N(R^9)_2$ and $-NR^9S(O)_2R^8$, and

wherein the aryl and heteroaryl groups of R^3 and R^6 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, R^7, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-C(O)N(R^9)_2$, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$ and $-NR^9S(O)_2R^8$;

R^4 and R^5 are each independently selected from H, halogen, -C(O)OR^7, -C(O)R^7, -C(O)N($R^{11}R^{12}$), -N($R^{11}R^{12}$), -N(R^9)$_2$, -NHN(R^9)$_2$, -SR^7, -$(CH_2)_n$OR^7, -$(CH_2)_n$$R^7$, -L$R^8$, -L$R^{10}$, -OL$R^8$, -OL$R^{10}$, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl,

wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, or C_3-C_8heterocycloalkyl groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, =O, -NO_2, -R^7, -OR^8, -C(O)R^8, -OC(O)R^8, -C(O)OR^8, -N(R^9)$_2$, -P(O)(OR^8)$_2$, -OP(O)(OR^8)$_2$, -P(O)(OR^{10})$_2$, -OP(O)(OR^{10})$_2$, -C(O)N(R^9)$_2$, -Si(R^8)$_3$, –S(O)$_2$$R^8$, –S(O)$R^8$, –S(O)$_2$N($R^9$)$_2$, and -N$R^9$S(O)$_2$$R^8$, and

wherein the aryl and heteroaryl groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, -R^7, -OR^8, -C(O)R^8, -OC(O)R^8, -C(O)OR^8, -N(R^9)$_2$, -P(O)(OR^8)$_2$, -OP(O)(OR^8)$_2$, -P(O)(OR^{10})$_2$, -OP(O)(OR^{10})$_2$, -C(O)N(R^9)$_2$, -Si(R^8)$_3$, –S(O)$_2$$R^8$, –S(O)$R^8$, –S(O)$_2$N($R^9$)$_2$, and -N$R^9$S(O)$_2$$R^8$;

or R^3 and R^4, or R^4 and R^5, or R^5 and R^6, when present on adjacent ring atoms, can optionally be linked together to form a 5-6 membered ring, wherein the 5-6 membered ring is optionally substituted with R^7;

each L is independently selected from a bond, -$(O(CH_2)_m)_t$-, C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene, wherein the C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene of L are each optionally substituted with 1 to 4 substituents independently selected from halogen, -R^8, -OR^8, -N(R^9)$_2$, -P(O)(OR^8)$_2$, -OP(O)(OR^8)$_2$, -P(O)(OR^{10})$_2$, and -OP(O)(OR^{10})$_2$;

R^7 is selected from H, C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, and C_3-C_8heterocycloalkyl,

wherein the C_1-C_6alkyl, C_3-C_8cycloalkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, or C_3-C_8heterocycloalkyl groups of R^7 are each optionally substituted with 1 to 3 R^{13} groups, and each R^{13} is independently selected from halogen, –CN,

=O, -LR^9, -LOR^9, -OLR^9, -LR^{10}, -LOR^{10}, -OLR^{10}, -LR^8, -LOR^8, -OLR^8, -LSR^8, -LSR^{10}, -$LC(O)R^8$, -$OLC(O)R^8$, -$LC(O)OR^8$, -$LC(O)R^{10}$, -$LOC(O)OR^8$, -$LC(O)NR^9R^{11}$, -$LC(O)NR^9R^8$, -$LN(R^9)_2$, -LNR^9R^8, -LNR^9R^{10}, -$LC(O)N(R^9)_2$, -$LS(O)_2R^8$, -$LS(O)R^8$, -$LC(O)NR^8OH$, -$LNR^9C(O)R^8$, -$LNR^9C(O)OR^8$, -$LC(=N\text{-}OR^8)R^8$, -$LC(=NH)\text{-}NHOR^8$, -$NHC(=NH)NH_2$, -$LS(O)_2N(R^9)_2$, -$OLS(O)_2N(R^9)_2$, -$LNR^9S(O)_2R^8$, -$LC(O)NR^9LN(R^9)_2$, -$LP(O)(OR^8)_2$, -$LOP(O)(OR^8)_2$, -$LP(O)(OR^{10})_2$ and -$OLP(O)(OR^{10})_2$;

wherein the aryl and heteroaryl groups of R^7 are each optionally substituted with 1 to 3 R^{13} groups, and each R^{13} is independently selected from halogen, –CN, -LR^9, -LOR^9, -OLR^9, -LR^{10}, -LOR^{10}, -OLR^{10}, -LR^8, -LOR^8, -OLR^8, -LSR^8, -LSR^{10}, -$LC(O)R^8$, -$OLC(O)R^8$, -$LC(O)OR^8$, -$LC(O)R^{10}$, -$LOC(O)OR^8$, -$LC(O)NR^9R^{11}$, -$LC(O)NR^9R^8$, -$LN(R^9)_2$, -LNR^9R^8, -LNR^9R^{10}, -$LC(O)N(R^9)_2$, -$LS(O)_2R^8$, -$LS(O)R^8$, -$LC(O)NR^8OH$, -$LNR^9C(O)R^8$, -$LNR^9C(O)OR^8$, -$LC(=N\text{-}OR^8)R^8$, -$LC(=NH)\text{-}NHOR^8$, -$NHC(=NH)NH_2$, -$LS(O)_2N(R^9)_2$, -$OLS(O)_2N(R^9)_2$, -$LNR^9S(O)_2R^8$, -$LC(O)NR^9LN(R^9)_2$, -$LP(O)(OR^8)_2$, -$LOP(O)(OR^8)_2$, -$LP(O)(OR^{10})_2$ and -$OLP(O)(OR^{10})_2$;

each R^8 is independently selected from H, -$CH(R^{10})_2$, C_1-C_8alkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, C_1-C_6hydroxyalkyl and C_1-C_6haloalkoxy, wherein the C_1-C_8alkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, C_1-C_6hydroxyalkyl and C_1-C_6haloalkoxy groups of R^8 are each optionally substituted with 1 to 3 substituents independently selected from –CN, R^{11}, -OR^{11}, -SR^{11}, -$C(O)R^{11}$, -$OC(O)R^{11}$, -$C(O)N(R^9)_2$, -$C(O)OR^{11}$, -$NR^9C(O)R^{11}$, -NR^9R^{10}, -$NR^{11}R^{12}$, -$N(R^9)_2$, -OR^9, -OR^{10}, -$C(O)NR^{11}R^{12}$, -$C(O)NR^{11}OH$, -$S(O)_2R^{11}$, -$S(O)R^{11}$, -$S(O)_2NR^{11}R^{12}$, -$NR^{11}S(O)_2R^{11}$, -$P(O)(OR^{11})_2$, and -$OP(O)(OR^{11})_2$;

each R^9 is independently selected from H, -$C(O)R^8$, -$C(O)OR^8$, -$C(O)R^{10}$, -$C(O)OR^{10}$, -$Si(R^8)_3$, -$S(O)_2R^{10}$, -C_1-C_6 alkyl, C_1-C_6 heteroalkyl and C_3-C_6 cycloalkyl, or each R^9 is independently a C_1-C_6alkyl that together with N they are attached to form a C_3-C_8heterocycloalkyl, wherein the C_3-C_8heterocycloalkyl ring optionally

contains an additional heteroatom selected from N, O and S, and wherein the C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, or C_3-C_8heterocycloalkyl groups of R^9 are each optionally substituted with 1 to 3 substituents independently selected from –CN, R^{11}, -OR^{11}, -SR^{11}, -$C(O)R^{11}$, -$OC(O)R^{11}$, -$C(O)OR^{11}$, -$NR^{11}R^{12}$, -$C(O)NR^{11}R^{12}$, -$C(O)NR^{11}OH$, -$S(O)_2R^{11}$, -$S(O)R^{11}$, -$S(O)_2NR^{11}R^{12}$, -$NR^{11}S(O)_2R^{11}$, -$P(O)(OR^{11})_2$, and -$OP(O)(OR^{11})_2$;

each R^{10} is independently selected from aryl, C_3-C_8cycloalkyl, C_3-C_8heterocycloalkyl and heteroaryl, wherein the aryl, C_3-C_8cycloalkyl, C_3-C_8heterocycloalkyl and heteroaryl groups are optionally substituted with 1 to 3 substituents selected from halogen, $–R^8$, -OR^8, $–LR^9$, -LOR^9, -$N(R^9)_2$, -$NR^9C(O)R^8$, -$NR^9CO_2R^8$, -CO_2R^8, -$C(O)R^8$ and -$C(O)N(R^9)_2$;

R^{11} and R^{12} are independently selected from H, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl,

wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl groups of R^{11} and R^{12} are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, =O, R^8, $–OR^8$, -$C(O)R^8$, -$OC(O)R^8$, -$C(O)OR^8$, -$N(R^9)_2$, -$NR^8C(O)R^8$, -$NR^8C(O)OR^8$, -$C(O)N(R^9)_2$, C_3-C_8heterocycloalkyl, $–S(O)_2R^8$, $–S(O)_2N(R^9)_2$, -$NR^9S(O)_2R^8$, C_1-C_6haloalkyl and C_1-C_6haloalkoxy, and

wherein the aryl and heteroaryl groups of R^{11} and R^{12} are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, R^8, $–OR^8$, -$C(O)R^8$, -$OC(O)R^8$, -$C(O)OR^8$, -$N(R^9)_2$, -$NR^8C(O)R^8$, -$NR^8C(O)OR^8$, -$C(O)N(R^9)_2$, C_3-C_8heterocycloalkyl, $–S(O)_2R^8$, -$S(O)_2N(R^9)_2$, -$NR^9S(O)_2R^8$, C_1-C_6haloalkyl and C_1-C_6haloalkoxy,

or R^{11} and R^{12} are each independently C_1-C_6alkyl and taken together with the N atom to which they are attached form an optionally substituted C_3-C_8heterocycloalkyl ring optionally containing an additional heteroatom selected from N, O and S;

Ring A is an aryl or a heteroaryl, wherein the aryl or heteroaryl groups of Ring A are optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from halogen, $–R^8$, $–R^7$, -OR^7, -OR^8, $–R^{10}$, -OR^{10}, -SR^8, -NO_2, -CN, -

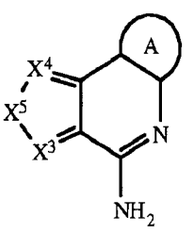
$N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$, and two adjacent substituents on Ring A can be joined to form a 5-6 membered ring that can contain up to two heteroatoms as ring members;

n is, independently at each occurrence, 0, 1, 2, 3, 4, 5, 6, 7 or 8;

each m is independently selected from 1, 2, 3, 4, 5 and 6, and

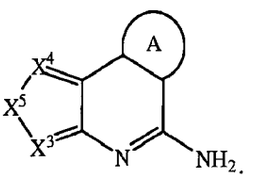
t is 1, 2, 3, 4, 5, 6, 7 or 8.

[000106] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (I-A),



Formula (I-A).

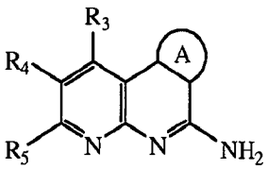
[000107] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (I-B),



Formula (I-B).

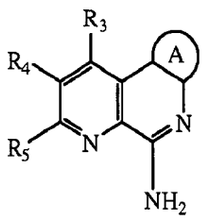
[000108] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of

Formula (II),



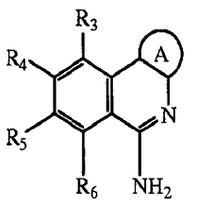
Formula (II).

[000109] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (III),



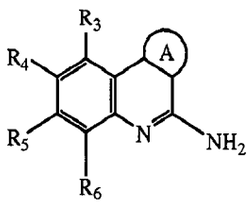
Formula (III).

[000110] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (IV),



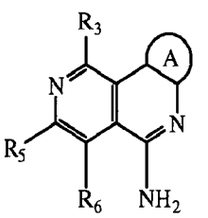
Formula (IV).

[000111] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (V),



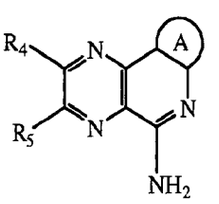
Formula (V).

[000112] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (VI),



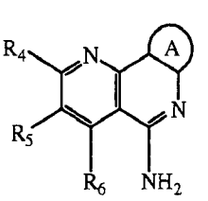
Formula (VI).

[000113] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (VII),



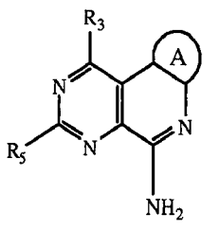
Formula (VII).

[000114] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (VIII),



Formula (VIII).

[000115] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (IX),



Formula (IX).

[000116] In certain embodiments of compounds of Formulas (I)-(IX), Formula (I-A) and Formula (I-B), ring A is selected from phenyl, naphthyl, fluorenyl, indenyl, azulenyl and anthracenyl, each of which is optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$. In other embodiments of compounds of Formulas (I)-(IX), Formula (I-A) and Formula (I-B), Ring A is phenyl or naphthyl, each of which is optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$.

[000117] In certain embodiments of compounds of Formulas (I)-(IX), Formula (I-A) and Formula (I-B), ring A is selected from benzofuranyl, benzofurazanyl, benzoxazolyl, benzopyranyl, benzthiazolyl, benzothienyl, benzazepinyl, benzimidazolyl, benzothiopyranyl, benzo[1,3]dioxole, benzo[b]furyl, benzo[b]thienyl, cinnolinyl, furazanyl, furyl, furopyridinyl, imidazolyl, indolyl, indolizinyl, indolin-2-one, indazolyl, isoindolyl, isoquinolinyl, isoxazolyl, isothiazolyl, 1,8-naphthyridinyl, oxazolyl, oxaindolyl, oxadiazolyl, pyrazolyl, pyrrolyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinoxalinyl, quinolinyl, quinazolinyl, 4H-quinolizinyl, thiazolyl, thiadiazolyl, thienyl, triazinyl,triazolyl and

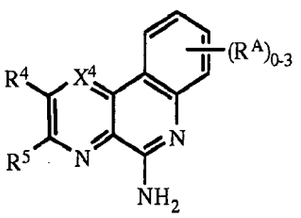
tetrazolyl, each of which is optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$. In other embodiments of compounds of Formulas (I)-(IX), Formula (I-A) and Formula (I-B), Ring A is selected from pyridyl, benzo[1,3]dioxole, thienyl, benzothienyl, benzofuranyl, or indolyl, each of which is optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$.

[000118] In certain embodiments of compounds of Formulas (I)-(IX), Formula (I-A) and Formula (I-B), Ring A is selected from phenyl, thienyl, and pyridyl, and in other embodiments such phenyl, thienyl, and pyridyl groups are optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$.

[000119] In certain embodiments of compounds of Formulas (I)-(IX), Formula (I-A) and Formula (I-B), Ring A is a phenyl optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$,

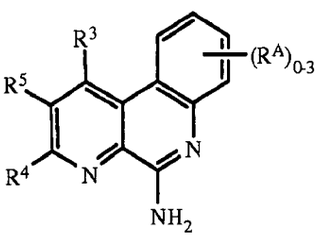
$-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$. In certain embodiments of compounds of Formulas (I)-(IX), Formula (I-A) and Formula (I-B), Ring A is a pyridyl optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$.

[000120] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (X),



Formula (X).

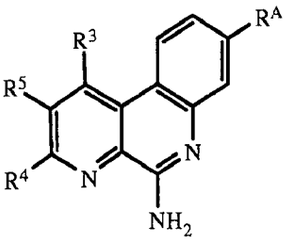
[000121] In certain embodiments compounds of Formula (X), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (X-A),



Formula (X-A).

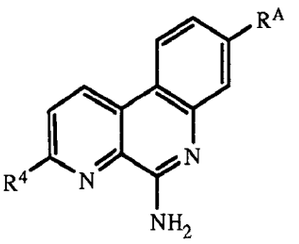
[000122] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives,

protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (XI),

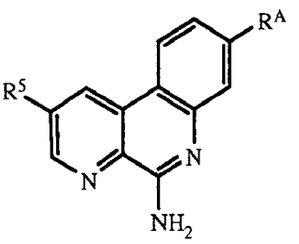


Formula (XI).

[000123] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (XII) or Formula (XIII),



Formula (XII)



Formula (XIII).

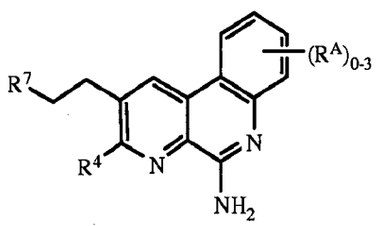
[000124] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIII), R^4 and R^5, when present, are independently selected from H, halogen, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-SR^7$, $-(CH_2)_nOR^7$, $-(CH_2)_nR^7$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, or C_3-C_8heterocycloalkyl groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, $-CN$, $=O$, $-NO_2$, $-R^7$, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-C(O)N(R^9)_2$, $-Si(R^8)_3$, $-S(O)_2R^8$, $-S(O)R^8$, $-S(O)_2N(R^9)_2$, and $-NR^9S(O)_2R^8$, and wherein the aryl and heteroaryl groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, $-CN$, $-R^7$, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-C(O)N(R^9)_2$, $-Si(R^8)_3$, $-S(O)_2R^8$, $-S(O)R^8$, $-S(O)_2N(R^9)_2$, and $-NR^9S(O)_2R^8$. In other embodiments, R^3 and R^4,

or R^4 and R^5, or R^5 and R^6, when present on adjacent ring atoms, can optionally be linked together to form a 5-6 membered ring, wherein the 5-6 membered ring is optionally substituted with R^7.

[000125] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIII), each L is independently selected from a bond, $-(O(CH_2)_m)_t-$, C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene, wherein the C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene of L are each optionally substituted with 1 to 4 substituents independently selected from halogen, $-R^8$, $-OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, and $-OP(O)(OR^{10})_2$.

[000126] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIII), R^4 and R^5, when present, are independently selected from H, halogen, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-SR^7$, $-(CH_2)_nOR^7$, $-(CH_2)_nR^7$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_3-C_8heterocycloalkyl, aryl and heteroaryl groups of R^4 and R^5 are each optionally substituted with 1 to 3 R^7.

[000127] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (XIV),



Formula (XIV).

[000128] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIV), R^7 is selected from H, C_1-C_6alkyl, C_3-C_8cycloalkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, C_3-C_8cycloalkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, and C_3-C_8heterocycloalkyl groups of R^7 are each optionally substituted with 1 to 3 R^{13} groups and each R^{13} is independently selected from halogen –CN, =O, $-LR^9$, $-LOR^9$, $-OLR^9$, $-LR^{10}$, $-LOR^{10}$, $-OLR^{10}$, $-LR^8$, $-LOR^8$, $-OLR^8$, $-LSR^8$, $-LSR^{10}$, $-LC(O)R^8$, $-OLC(O)R^8$, $-LC(O)OR^8$, $-LC(O)R^{10}$, $-LOC(O)OR^8$, $-LC(O)NR^9R^{11}$, $-LC(O)NR^9R^8$, $-LN(R^9)_2$, $-LNR^9R^8$, $-LNR^9R^{10}$, -

$LC(O)N(R^9)_2$, $-LS(O)_2R^8$, $-LS(O)R^8$, $-LC(O)NR^8OH$, $-LNR^9C(O)R^8$, $-LNR^9C(O)OR^8$, $-LC(=N-OR^8)R^8$, $-LC(=NH)-NHOR^8$, $-NHC(=NH)NH_2$, $-LS(O)_2N(R^9)_2$, $-OLS(O)_2N(R^9)_2$, $-LNR^9S(O)_2R^8$, $-LC(O)NR^9LN(R^9)_2$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$ and $-OLP(O)(OR^{10})_2$.

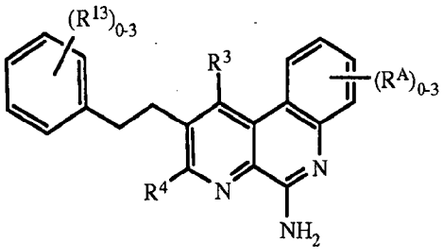
[000129] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIV), R^7 is an aryl or heteroaryl group optionally substituted with 1 to 3 R^{13} groups and each R^{13} is independently selected from halogen, –CN, $-LR^9$, $-LOR^9$, $-OLR^9$, $-LR^{10}$, $-LOR^{10}$, $-OLR^{10}$, $-LR^8$, $-LOR^8$, $-OLR^8$, $-LSR^8$, $-LSR^{10}$, $-LC(O)R^8$, $-OLC(O)R^8$, $-LC(O)OR^8$, $-LC(O)R^{10}$, $-LOC(O)OR^8$, $-LC(O)NR^9R^{11}$, $-LC(O)NR^9R^8$, $-LN(R^9)_2$, $-LNR^9R^8$, $-LNR^9R^{10}$, $-LC(O)N(R^9)_2$, $-LS(O)_2R^8$, $-LS(O)R^8$, $-LC(O)NR^8OH$, $-LNR^9C(O)R^8$, $-LNR^9C(O)OR^8$, $-LC(=N-OR^8)R^8$, $-LC(=NH)-NHOR^8$, $-NHC(=NH)NH_2$, $-LS(O)_2N(R^9)_2$, $-OLS(O)_2N(R^9)_2$, $-LNR^9S(O)_2R^8$, $-LC(O)NR^9LN(R^9)_2$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$ and $-OLP(O)(OR^{10})_2$.

[000130] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIV), R^7 is selected from H, C_1-C_6alkyl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, and the C_1-C_6alkyl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl groups are each optionally substituted with 1-3 R^{13} groups and each R^{13} is independently selected from halogen, =O, C_1-C_6haloalkyl, LR^8, LR^9, OLR^8 and $-LOR^8$.

[000131] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIV), R^7 is an aryl or heteroaryl group optionally substituted with 1-3 R^{13} groups and each R^{13} is independently selected from halogen, C_1-C_6haloalkyl, LR^8, LR^9, OLR^8 and $-LOR^8$.

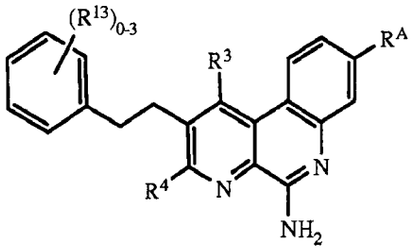
[000132] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIV), each L is independently selected from a bond, $-(O(CH_2)_m)_t-$, C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene, wherein the C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene of L are each optionally substituted with 1 to 4 substituents independently selected from halogen, $-R^8$, $-OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, and $-OP(O)(OR^{10})_2$.

[000133] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (XV),



Formula (XV).

[000134] In certain embodiments compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure of Formula (XVI),



Formula (XVI).

[000135] In certain compounds of Formula (XV) or (XVI), R^4, R^A and R^{13} are independently selected from H, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH_2OH$, $-OCH_3$, $-COOCH_3$, $-COOCH_2CH_3$, F, Cl, Br, $-CH_2OCH_3$, $CH_2OCH_2CH_3$, $-N(CH_3)_2$, $-((O(CH_2)_2)_{2-4}OH$, $-O(CH_2)_{2-4}-OH$, $-O(CH_2)_{2-4}-(PO_3H_2)$, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}-CH(CH_3)_2$, C_2-C_6 alkyl substituted with 1-3 substituents selected from –OH, $-CH_3$, cyclopropyl, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}(PO_3H_2)$, -COOH, $COOCH_3$, and $-COOCH_2CH_3$. In some embodiments of such compounds, R^4 is H. In certain of these compounds, the phenyl ring of the phenethyl group has one to three R^{13} groups. Optionally, R^A is H or $-CH_3$. In certain embodiments, these compounds have two R^{13} groups present, and those R^{13} groups are selected from the group consisting of of $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH_2OH$, $-OCH_3$, $-COOCH_3$, $-COOCH_2CH_3$, F, Cl, Br, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-N(CH_3)_2$, $-((O(CH_2)_2)_{2-4}OH$, $-O(CH_2)_{2-4}-OH$, $-O(CH_2)_{2-4}-(PO_3H_2)$, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}-CH(CH_3)_2$, C_2-C_6 alkyl substituted with 1-3 substituents selected from –OH, $-CH_3$, cyclopropyl, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}(PO_3H_2)$, -COOH, $COOCH_3$, and $-COOCH_2CH_3$.

[000136] In certain embodiments of the compounds of Formula XIII, XIV, XV or XVI, the

compound is selected from: 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 2-(4-(dimethylamino)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine, and 2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine. Each of these compounds individually comprises a preferred embodiment of the compounds, compositions, and methods described herein.

[000137] In certain embodiments compounds of Formula (I) as described herein are combined with an antigen, and optionally a carrier, pharmaceutically acceptable excipient or adjuvant, to provide an immunogenic composition. In certain embodiments compounds of Formula (XVI) as described herein are combined with an antigen, and optionally a carrier, pharmaceutically acceptable excipient or adjuvant, to provide an immunogenic composition. In other embodiments, such immunogenic composition comprise a compound of Formula (I) and an antigen, wherein the antigen includes, but is not limited to, a bacterial antigen, a viral antigen, a fungal antigen, a tumor antigen, or an antigen associated with an STD, Alzheimer's, respiratory disorders, autoimmune disorders such as, by way of example only, rheumatoid arthritis or lupus, pediatric disorders and obesity, and wherein the amount of the compound is an amount effective to enhance an immune response to the antigen in a subject to whom the composition is administered. In other embodiments, such immunogenic composition comprise a compound of Formula (XVI) and an antigen, wherein the antigen includes, but is not limited to, a bacterial antigen, a viral antigen, a fungal antigen, a tumor antigen, or an antigen associated with an STD, Alzheimer's, respiratory disorders, autoimmune disorders such as, by way of example only, rheumatoid arthritis or lupus, pediatric disorders and obesity, and wherein the amount of the compound is an amount effective to enhance an immune response to the antigen in a subject to whom the composition is administered. Suitable antigens for use in such immunogenic compositions are described herein.

[000138] In certain embodiments, such immunogenic compositions include a bacterial antigen of a strain of *Neisseria meningitides*, such as serogroup A, C, W135, Y and/or B. Specific antigens for use in these compositions are described herein. In other embodiments, such immunogenic compositions, and others provided herein, are used as vaccines; their use in the treatment of disorders associated with the antigen included in the composition is described herein.

[000139] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XVI), each R^{13} is independently selected from LR^{10}, LOR^{10}, LR^8, $-LOR^8$, $-LSR^8$, LSR^{10}, $-LC(O)OR^8$, $-LN(R^9)_2$, $-LC(O)N(R^9)_2$, $-LS(O)_2R^8$, $-LS(O)R^8$, $-LP(O)(OR^8)_2$, $-OLP(O)(OR^8)_2$, $-LP(O)(O\,R^{10})_2$ and $-OLP(O)(OR^{10})_2$.

[000140] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XVI), each L is independently selected from a bond, $-(O(CH_2)_m)_t-$, C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene, wherein the C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene of L are each optionally substituted with 1 to 4 substituents independently selected from halogen, $-R^8$, $-OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, and $-OP(O)(OR^{10})_2$.

[000141] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XVI), R^1 and R^2 are each H.

[000142] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XVI), R^3 and R^6, when present, are independently selected from H, halogen, C_1-C_6alkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy.

[000143] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XVI), R^{10} is an aryl or a heteroaryl, wherein the aryl and heteroaryl groups are optionally substituted with 1 to 3 substituents selected from halogen, $-R^8$, $-OR^8$, LR^9 and $-N(R^9)_2$. In other embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XVI), R^{10} is phenyl optionally substituted with 1 to 3 substituents selected from halogen, $-R^8$, $-OR^8$, and $-N(R^9)_2$.

[000144] In certain embodiments of compounds of Formulas (I), (I-A), (I-B) and (II)-(XIII), R^8 is selected from H, C_1-C_6alkyl and C_1-C_6haloalkyl.

[000145] In certain embodiments the compound of Formulas (I) is 3-chloro-2-methylbenzo[f][1,7]naphthyridin-5-amine; 2-methylbenzo[f][1,7]naphthyridin-5-amine; pyrimido[4,5-c]quinolin-5-amine; 2-(ethoxymethyl)benzo[f][1,7]naphthyridin-5-amine; pyrimido[4,5-c]quinoline-3,5-diamine; 3-(methylthio)pyrimido[4,5-c]quinolin-5-amine; (E)-2-(2-cyclopropylvinyl)benzo[f][1,7]naphthyridin-5-amine; (E)-2-(pent-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 4-(5-aminobenzo[f][1,7]naphthyridin-2-yl)-2-methylbut-3-yn-2-ol; 2-pentylbenzo[f][1,7]naphthyridin-5-amine; (E)-2-(prop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; (E)-2-(3-phenylprop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-cyclopropylethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(5-aminobenzo[f][1,7]naphthyridin-2-yl)-2-methylbutan-2-ol; 2-propylbenzo[f][1,7]naphthyridin-5-amine; 2-(3-phenylpropyl)benzo[f][1,7]naphthyridin-5-amine; 2-ethylbenzo[f][1,7]naphthyridin-5-

amine; 2-(2-methylprop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 2-isobutylbenzo[f][1,7]naphthyridin-5-amine; (E)-2-(2,4-difluorostyryl)benzo[f][1,7]naphthyridin-5-amine; (E)-2-(hex-1-enyl)benzo[f][1,7]naphthyridin-5-amine; (E)-2-(2-cyclohexylvinyl)benzo[f][1,7]naphthyridin-5-amine; E)-2-(3-(trifluoromethyl)styryl)benzo[f][1,7]naphthyridin-5-amine; (E)-2-(3-methoxystyryl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-vinylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-methyl-2-styrylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-cyclohexylethyl)benzo[f][1,7]naphthyridin-5-amine; 2-fluorobenzo[f][1,7]naphthyridin-5-amine; 2-(3-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-difluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-hexylbenzo[f][1,7]naphthyridin-5-amine; 2-ethyl-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; methyl 5-aminobenzo[f][1,7]naphthyridine-3-carboxylate; 5-amino-N-methylbenzo[f][1,7]naphthyridine-3-carboxamide; (5-aminobenzo[f][1,7]naphthyridin-3-yl)methanol; 8-phenylbenzo[f][1,7]naphthyridin-5-amine; 3-(ethoxymethyl)benzo[f][1,7]naphthyridin-5-amine; benzo[f][1,7]naphthyridine-3,5-diamine; benzo[f][1,7]naphthyridin-5-amine; methyl 5-aminobenzo[f][1,7]naphthyridine-8-carboxylate; 5-aminobenzo[f][1,7]naphthyridine-8-carboxylic acid; ethyl 5-aminobenzo[f][1,7]naphthyridine-8-carboxylate; (5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol; 5-aminobenzo[f][1,7]naphthyridine-3-carboxylic acid; 5-aminobenzo[f][1,7]naphthyridine-3-carbaldehyde; 2-(o-tolylethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-(m-tolylethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-(p-tolylethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 3-chloro-2-(ethoxymethyl)benzo[f][1,7]naphthyridin-5-amine; pyrazino[2,3-c]quinolin-5-amine; 9-chlorobenzo[f][1,7]naphthyridin-5-amine; 8-chlorobenzo[f][1,7]naphthyridin-5-amine; 9-methylbenzo[f][1,7]naphthyridin-5-amine; 10-methylbenzo[f][1,7]naphthyridin-5-amine; ethyl 5-aminobenzo[f][1,7]naphthyridine-9-carboxylate; 5-aminobenzo[f][1,7]naphthyridine-9-carboxylic acid; 8-methoxybenzo[f][1,7]naphthyridin-5-amine; 7-fluorobenzo[f][1,7]naphthyridin-5-amine; 8-(methylsulfonyl)benzo[f][1,7]naphthyridin-5-amine; 8-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine; 8-fluorobenzo[f][1,7]naphthyridin-5-amine;

3-methoxybenzo[f][1,7]naphthyridin-5-amine; 3-butoxybenzo[f][1,7]naphthyridin-5-amine; 3-(benzyloxy)benzo[f][1,7]naphthyridin-5-amine; 3-methylbenzo[f][1,7]naphthyridin-5-amine; 3-chlorobenzo[f][1,7]naphthyridin-5-amine; N^3,N^3-dimethylbenzo[f][1,7]naphthyridine-3,5-diamine; N^3-butylbenzo[f][1,7]naphthyridine-3,5-diamine; 3-vinylbenzo[f][1,7]naphthyridin-5-amine; 3-ethylbenzo[f][1,7]naphthyridin-5-amine; 3-fluorobenzo[f][1,7]naphthyridin-5-amine; 2-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine; 2-methoxybenzo[f][1,7]naphthyridin-5-amine; 2-(benzyloxy)benzo[f][1,7]naphthyridin-5-amine; 2-vinylbenzo[f][1,7]naphthyridin-5-amine; 2-phenylbenzo[f][1,7]naphthyridin-5-amine; (E)-2-styrylbenzo[f][1,7]naphthyridin-5-amine; 2-phenethylbenzo[f][1,7]naphthyridin-5-amine; (E)-2-(3-methoxyprop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-methoxypropyl)benzo[f][1,7]naphthyridin-5-amine; 2-(prop-1-en-2-yl)benzo[f][1,7]naphthyridin-5-amine; 2-isopropylbenzo[f][1,7]naphthyridin-5-amine; 1-methylbenzo[f][1,7]naphthyridin-5-amine; benzo[c][1,8]naphthyridin-6-amine; pyrido[3,2-f][1,7]naphthyridin-6-amine; thieno[2,3-c]quinolin-4-amine; 8-methyl-2-(naphthalen-2-ylethynyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(naphthalen-1-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(naphthalen-2-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(naphthalen-1-ylethynyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoic acid; 3-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoic acid; 2-(3-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (3-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol; 2-(4-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-(trifluoromethyl)phenanthridin-6-amine; benzo[c][2,7]naphthyridin-5-amine; 2-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine; 2-tert-butoxybenzo[f][1,7]naphthyridin-5-amine; 5-aminobenzo[f][1,7]naphthyridin-2-ol; 2-((4-butylphenyl)ethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-butylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-benzyl-5-chloro-7-(trifluoromethyl)-1,2-dihydropyrido[3,4-b]pyrazin-3(4H)-one; 2-(2-(6-methoxynaphthalen-2-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-butylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-propylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,5-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-propylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2,4,5-

trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,5-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-isopropylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-heptylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (Z)-2-(2-(biphenyl-4-yl)vinyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-isobutoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-((2-methoxyethoxy)methoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-phenoxyethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(tert-butyldimethylsilyloxy)ethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-butoxy-2-methylphenethyl)-N-butyl-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-phenylbutoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(allyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(3-phenylpropoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(heptan-4-yloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-methylpent-3-enyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-cyclohexylethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-isopropoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(3,3-dimethylbutoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(tert-butyldimethylsilyloxy)ethoxy)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; diethyl 3-(2-(4-(2-(2-hydroxyethoxy)ethoxy)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-ylamino)propylphosphonate; (E)-N-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)vinyl)phenyl)acetamide; N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide; N-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide; N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-4-methylbenzenesulfonamide; 3-methyl-9-p-tolyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzonitrile; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-aminoethyl)-3-methylbenzamide; 2-(4-(2-(5-amino-3-chloro-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetic acid; (S)-2-(4-(2-(5-amino-3-chloro-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoic acid; 4-(2-

(5-amino-3-chloro-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide; 8-methyl-2-(2-methyl-4-(1H-tetrazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; methyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoate; methyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetic acid; 6-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)hexan-1-ol; 7-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)heptanoic acid; 11-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)undecan-1-ol; 2-phenethylbenzo[f][1,7]naphthyridin-5-amine; ethyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)acetate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)acetic acid; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propanoic acid; 6-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)hexanoic acid; 8-methyl-2-(2-methyl-4-(methylthio)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(methylsulfonyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(hexyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-phenethoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-cyclobutoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(pentyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-methylpentyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-bromo-3-methoxybenzo[f][1,7]naphthyridin-5-amine; 2-((tert-butyldimethylsilyl)ethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-((2-fluorophenyl)ethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-((3-fluorophenyl)ethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-((4-fluorophenyl)ethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-(thiophen-3-ylethynyl)benzo[f][1,7]naphthyridin-5-amine; 2-ethynylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(thiophen-3-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; ethyl 5-aminobenzo[f][1,7]naphthyridine-2-

carboxylate; ethyl 5-amino-8-methylbenzo[f][1,7]naphthyridine-2-carboxylate; (5-aminobenzo[f][1,7]naphthyridin-2-yl)methanol; 2-(3,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-chloro-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-1-(3-phenylpropyl)benzo[f][1,7]naphthyridin-5-amine; (Z)-2-(2-(benzo[d][1,3]dioxol-5-yl)vinyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (Z)-2-(4-methoxy-2-methylstyryl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(3,4-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(3,5-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(1-phenylvinyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-phenylbutyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(1-phenylethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(benzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (Z)-2-(2-ethoxyvinyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-ethoxyethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(chloromethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-nitroethyl)benzo[f][1,7]naphthyridin-5-amine; diethyl 2-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)methyl)malonate; 2-(isopropylsulfonyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-((methoxymethoxy)methyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-((methylamino)methyl)benzo[f][1,7]naphthyridin-5-amine; tert-butyl 5-amino-8-methylbenzo[f][1,7]naphthyridin-2-ylcarbamate; 8-methyl-2-((phenylamino)methyl)benzo[f][1,7]naphthyridin-5-amine; 2-(aminomethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(pyrrolidin-1-ylmethyl)benzo[f][1,7]naphthyridin-5-amine; N^2-(2,4-dimethoxybenzyl)-8-methylbenzo[f][1,7]naphthyridine-2,5-diamine; N^2,N^2,8-trimethylbenzo[f][1,7]naphthyridine-2,5-diamine; N^2,8-dimethylbenzo[f][1,7]naphthyridine-2,5-diamine; 8-methyl-2-(pyrrolidin-1-yl)benzo[f][1,7]naphthyridin-5-amine; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-phenylethanol; 2-(2-aminoethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-hydrazinyl-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-2-methylpropan-2-ol; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(4-methoxyphenyl)ethanol; 2-(biphenyl-2-yl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,6-dimethylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(5-methoxypyridin-2-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoic acid; 5-(2-(5-amino-8-

methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-4-methylpyridin-2(1H)-one; 6-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)pyridin-3-ol; 3-methyldibenzo[b,f][1,7]naphthyridin-6-amine; 8-methyl-2-(4-(trifluoromethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,3-dihydro-1H-inden-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,3-dihydro-1H-inden-5-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; (E)-3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylic acid; (E)-ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylate; N^3,N^5-dibutylbenzo[f][1,7]naphthyridine-3,5-diamine; 8-(prop-1-en-2-yl)benzo[f][1,7]naphthyridin-5-amine; 5-aminobenzo[f][1,7]naphthyridine-8-carbonitrile; (E)-8-(3-methylbut-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-methylprop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; (E)-8-(pent-1-enyl)benzo[f][1,7]naphthyridin-5-amine; (E)-8-styrylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-(2-cyclopropylvinyl)-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; 8-pentylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-(2-cyclopropylvinyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; pyrido[1,2-c][1,7]naphthyridin-6-amine; 9-phenethylpyrido[1,2-c][1,7]naphthyridin-6-amine; methyl 5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridine-8-carboxylate; 8-nitrobenzo[f][1,7]naphthyridin-5-amine; 3-chloro-8-methylbenzo[f][1,7]naphthyridin-5-amine; methyl 5-amino-3-chlorobenzo[f][1,7]naphthyridine-8-carboxylate; methyl 5-amino-3-fluorobenzo[f][1,7]naphthyridine-8-carboxylate; 3-chloro-8-nitrobenzo[f][1,7]naphthyridin-5-amine; (5-amino-3-chlorobenzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-phenethylbenzo[f][1,7]naphthyridin-8-yl)methanol; 4-(2-(5-amino-8-fluorobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzaldehyde; 2-(4-(2-(5-amino-8-fluorobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzylamino)ethanol; 3-(4-(2-(5-amino-8-fluorobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzylamino)propan-1-ol; 8-fluoro-2-(4-((2-methoxyethylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-((tert-butyldimethylsilyloxy)methyl)-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 3-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol; 2-(2-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-ethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-ethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-

(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(piperidin-1-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-tert-butylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(piperidin-1-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(3,5-dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(1-methyl-1H-imidazol-5-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-hydroxybenzimidamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzonitrile; 8-methyl-2-(4-(1-morpholinoethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-aminophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)guanidine; 8-methyl-2-(4-(1-(phenethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetonitrile; 2-(4-(piperidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzyl)piperidin-4-ol; 2-(4-(aminomethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-((ethylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-aminopropan-2-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-(1-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid; 8-methyl-2-(4-(1-(phenylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-ethyl-8-methylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)methanol; 8-methyl-2-propylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(1H-indol-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-ethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-phenoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol; 2-(2-(2,3-dihydrobenzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-

yl)ethanol; 3-methyl-9-phenyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine; 8-methylbenzo[f][1,7]naphthyridine-2,5-diamine; 1-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)propan-2-ol; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetonitrile; N-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetamide; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(2,4-dimethylphenyl)ethanol; 2-(2-(6-methoxy-4-methylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)butan-1-ol; methyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoate; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-1-ol; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-2-methylbutan-2-ol; 2-(4-(aminomethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (E)-ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylate; ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzyl)propane-1,3-diol; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoic acid; 5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridine-8-carbaldehyde; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoate; 8-methyl-2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-2-ol; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoic acid; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)methanol; 8-methyl-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 8-methyl-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; (E)-ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylate; (E)-3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylic acid; ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoate; 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoic acid; 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propan-1-ol; (5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol; 5-aminobenzo[f][1,7]naphthyridin-8-ol; 5-aminobenzo[f][1,7]naphthyridine-8-

carbaldehyde; 1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanol; 1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanone; 8-isopropylbenzo[f][1,7]naphthyridin-5-amine; 8-vinylbenzo[f][1,7]naphthyridin-5-amine; 8-ethylbenzo[f][1,7]naphthyridin-5-amine; 8-(methoxymethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-phenethylbenzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; benzo[f][1,7]naphthyridine-5,8-diamine; 8-(aminomethyl)benzo[f][1,7]naphthyridin-5-amine; 3-fluoro-8-methylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-3-fluorobenzo[f][1,7]naphthyridin-8-yl)methanol; 3-chlorobenzo[f][1,7]naphthyridine-5,8-diamine; 3-fluorobenzo[f][1,7]naphthyridine-5,8-diamine; 8-isobutylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-(prop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 8-propylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)benzo[f][1,7]naphthyridin-5-amine; 8-phenethylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(4-bromophenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 2-(4-methoxy-2-methylphenethyl)-8-pentylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; (2-(2-(1H-indol-5-yl)ethyl)-5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol; N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide; methyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,3-dimethylbenzamide; N-(2-acetamidoethyl)-4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide; 2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,N,3-trimethylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-hydroxyethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-3-methylbenzamide; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(pyrrolidin-1-yl)methanone; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(diethylamino)ethyl)-3-methylbenzamide; (4-(2-(5-amino-8-

methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(4-ethylpiperazin-1-yl)methanone; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(piperazin-1-yl)methanone; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methyl-N-(2-(pyrrolidin-1-yl)ethyl)benzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-aminoethyl)-3-methylbenzamide; 4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N-methylbenzamide; 2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 2-(4-butoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(biphenyl-4-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-((1,3-dihydroisobenzofuran-1-yl)methyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-methylallyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(isopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl propyl carbonate; ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoate; 2-(4-(cyclopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(cyclobutylmethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-1-phenylethanone; 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)ethanol; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-N,N-dimethylacetamide; 8-methyl-2-(2-methyl-4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethanol; diethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonate; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonic acid; 2-(4-butoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol; 2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol; ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoate; 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-

3-methylphenoxy)ethanol; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl ethyl carbonate; methyl 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoate; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoic acid; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)butanoic acid; 2-(4-(isopentyloxy)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl hexyl carbonate; 2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; diethyl 3-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)propylphosphonate; diethyl 3-(2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethoxy)propylphosphonate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl dimethylsulfamate; (5-amino-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 2-(4-(dimethylamino)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone; 2-(4-((dimethylamino)methyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(1-(dimethylamino)ethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone oxime; 8-methyl-2-(4-((methylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzylamino)ethanol; 8-methyl-2-(4-(pyrrolidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3,4-dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)ethanol; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanol; 8-methyl-2-(4-(oxazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propanenitrile; (2R)-2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propan-1-ol; 8-methyl-2-(4-(1-(piperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; ((2S)-1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidin-2-yl)methanol; N^1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^2,N^2-dimethylethane-1,2-diamine; 3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-

yl)ethyl)phenyl)ethylamino)propanoic acid; 8-methyl-2-(4-(1-(4-methylpiperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; N^2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^1,N^1-dimethylpropane-1,2-diamine; 8-methyl-2-(4-(1-(2-(pyridin-4-yl)ethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; N^1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^2,N^2-diethylethane-1,2-diamine; 2-(4-(dimethylamino)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid; 4-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)phenol; 1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2 yl)ethyl)phenyl)ethyl)pyrrolidin-3-ol; and 2-(4-(2-aminopropan-2-yl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine.

[000146] The compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein also includes all suitable isotopic variations of such compounds, and pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions. An isotopic variation of a compound provided herein or a pharmaceutically acceptable salt thereof is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that may be incorporated into the compounds provided herein and pharmaceutically acceptable salts thereof include but are not limited to isotopes of hydrogen, carbon, nitrogen and oxygen such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{35}S, ^{18}F, ^{36}Cl and ^{123}I. Certain isotopic variations of the compounds provided herein and pharmaceutically acceptable salts thereof, for example, those in which a radioactive isotope such as ^{3}H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. In particular examples, ^{3}H and ^{14}C isotopes may be used for their ease of preparation and detectability. In other examples, substitution with isotopes such as ^{2}H may afford certain therapeutic advantages resulting from greater metabolic stability, such as increased in vivo half-life or reduced dosage requirements. Isotopic variations of the compounds, and pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are prepared by conventional procedures using appropriate isotopic variations of suitable reagents.

Processes for Making Compounds of Formula (I)

[000147] General procedures for preparing compounds of Formula (I) are described in the

Examples, *infra*. In the reactions described, reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, may be protected to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice (see e.g., T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry," John Wiley and Sons, 1991).

[000148] In certain embodiments, the compounds of Formula (I) described herein are prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound of Formula (I) with a pharmaceutically acceptable organic acid or inorganic acid. In other embodiments, a pharmaceutically acceptable base addition salt of compounds of Formula (I) described herein is prepared by reacting the free acid form of the compound of Formula (I) with a pharmaceutically acceptable organic base or inorganic base. Alternatively, the salt forms of the compounds of Formula (I) described herein are prepared using salts of the starting materials or intermediates. In certain embodiments, the compounds of Formula (I) described herein are in the form of other salts including, but not limited to, oxalates and trifluoroacetates. In certain embodiments, hemisalts of acids and bases are formed, for example, hemisulphate and hemicalcium salts.

[000149] Such pharmaceutically acceptable acid addition salts of compounds of Formula (I) include, but are not limited to, a hydrobromide, hydrochloride, sulfate, nitrate, succinate, maleate, formate, acetate, adipate, besylatye, bicarbonate/carbonate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, naphthalenesulfonate (e.g. 2-naphthalenesulfonate), hexanoate salt, bisulphate/sulphate, borate, camsylate, cyclamate, edisylate, esylate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, tannate, tosylate, trifluoroacetate and xinofoate salts.

[000150] The organic acid or inorganic acids used to form certain pharmaceutically acceptable acid addition salts of compounds of Formula (I) include, but are not limited to, hydrobromic, hydrochloric, sulfuric, nitric, phosphoric, succinic, maleic, formic, acetic, propionic, fumaric, citric, tartaric, lactic, benzoic, salicylic, glutamic, aspartic, p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, naphthalenesulfonic such as 2-naphthalenesulfonic, or hexanoic

acid.

[000151] Such pharmaceutically acceptable base addition salt of a compound of Formula (I) include, but are not limited to, aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

[000152] In certain embodiments, the free acid or free base forms of the compounds of Formula (I) described herein are prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound Formula (I) in an acid addition salt form is converted to the corresponding free base by treating with a suitable base (by way of example only, an ammonium hydroxide solution, a sodium hydroxide, and the like). For example, a compound of Formula (I) in a base addition salt form is converted to the corresponding free acid by treating with a suitable acid (by way of example only, hydrochloric acid).

[000153] In certain embodiments, compounds of Formula (I) in unoxidized form are prepared from N-oxides of compounds Formula (I) by treating with a reducing agent (by way of example only, sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (by way of example only, acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

[000154] In certain embodiments, prodrug derivatives of compounds Formula (I) are prepared using methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs are prepared by reacting a non-derivatized compound of Formula (I) with a suitable carbamylating agent (by way of example only, 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

[000155] In certain embodiments, compounds of Formula (I) are prepared as protected derivatives using methods known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry," 3rd edition, John Wiley and Sons, Inc., 1999.

[000156] In certain embodiments, compounds of Formula (I) are prepared or formed, as solvates (e.g., hydrates). In certain embodiments, hydrates of compounds of Formula (I) are prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[000157] In certain embodiments, compounds of Formula (I) are prepared as their individual

stereoisomers. In other embodiments, the compounds of Formula (I) described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In certain embodiments, resolution of enantiomers is carried out using covalent diastereomeric derivatives of the compounds of Formula (I), or by using dissociable complexes (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubility, reactivity, etc.) and are readily separated by taking advantage of these dissimilarities. In certain embodiments, the diastereomers are separated by chromatography, or by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions," John Wiley And Sons, Inc., 1981.

[000158] Compounds of Formula (I) are made by processes described herein and as illustrated in the Examples. In certain embodiments, compounds of Formula (I) are made by:

(a) optionally converting a compound of Formula (I) into a pharmaceutically acceptable salt;

(c) optionally converting a salt form of a compound of Formula (I) to a non-salt form;

(d) optionally converting an unoxidized form of a compound of Formula (I) into a pharmaceutically acceptable N-oxide;

(e) optionally converting an N-oxide form of a compound of Formula (I) to its unoxidized form;

(f) optionally resolving an individual isomer of a compound of Formula (I) from a mixture of isomers;

(g) optionally converting a non-derivatized compound of Formula (I) into a pharmaceutically acceptable prodrug derivative; and

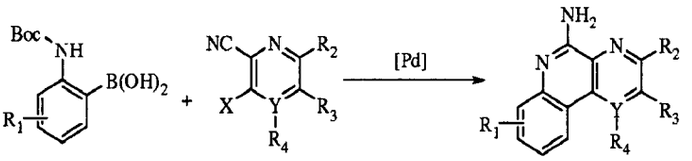
(h) optionally converting a prodrug derivative of a compound of Formula (I) to its non-derivatized form.

[000159] Non-limiting examples of synthetic schemes used to make compounds of Formula (I) described herein are illustrated in reaction schemes (I)-(XI).

[000160] Scheme (I) illustrates the synthesis of benzonaphthyridines (**3**) by coupling substituted or unsubsubstituted 2-(*tert*-butoxycarbonyl-amino)phenylboronic acids (**1**) with substituted or

unsubsubstituted 3-halopicolinonitrile derivatives (**2**) in the presence of a palladium catalyst. By way of example only, the halo moiety of the 3-halopicolinonitrile derivatives is bromo or chloro. The functional groups (R_1, R_2, R_3, R_4) on benzonaphthyridines (**3**) are optionally further modified, as described herein.

Scheme (I)

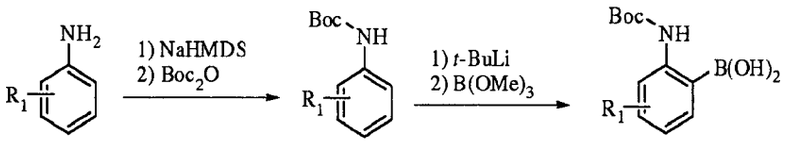


1 **2** **3**

X = Br or Cl
Y = C or N

[000161] In certain embodiments, the phenyl boronic acids used in the synthesis of compounds of Formula (I) were synthesized according to scheme (II). In scheme (II) substituted or unsubsubstituted anilines (**4**) are Boc-protected under basic conditions to give (**5**), and then converted into the boronic acids (**1**) through ortho-lithiation and reaction with trimethyl borate followed by aqueous workup.

Scheme (II)



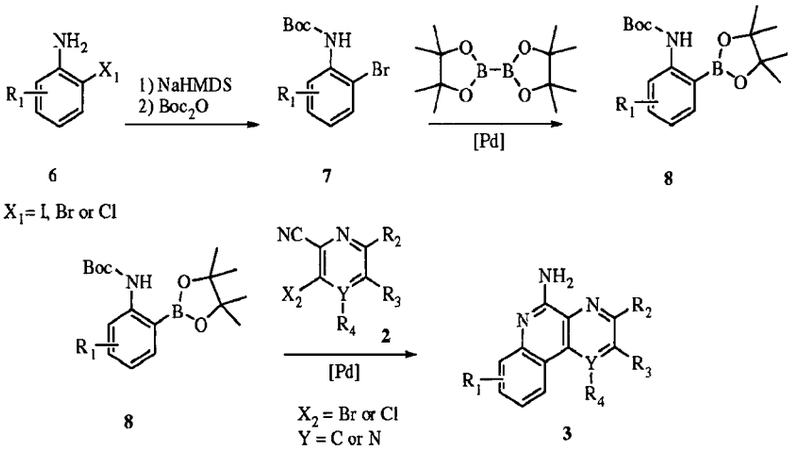
4 **5** **1**

[000162] Boric acids (**1**) are used as in scheme (I) and reacted with substituted or unsubsubstituted cyanopyridines (**2**) to afford substituted or unsubsubstituted benzonaphthyridines (**3**).

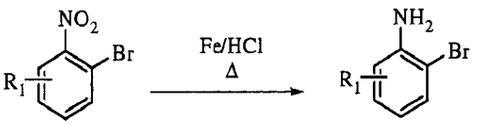
[000163] In certain embodiments, boronic acid equivalents including, but not limited to, substituted or unsubstituted boronate esters were used in the synthesis of compounds of Formula (I). Scheme (III) illustrates the synthesis of such substituted or unsubsubstituted boronate esters (**8**), which were used as boronic acid equivalents in the synthesis of substituted or unsubsubstituted benzonaphthyridines (**3**). In scheme (III) substituted or unsubsubstituted 2-haloanilines (**6**) are Boc-protected under basic conditions to give (**7**), which are then converted into the substituted or unsubsubstituted boronate esters (**8**) using palladium-mediated catalysis. These boronate esters (**8**) are used as in scheme (I) and react with substituted or unsubsubstituted cyanopyridines (**2**) to

afford substituted or unsubsubstituted benzonaphthyridines (**3**).

Scheme (III)

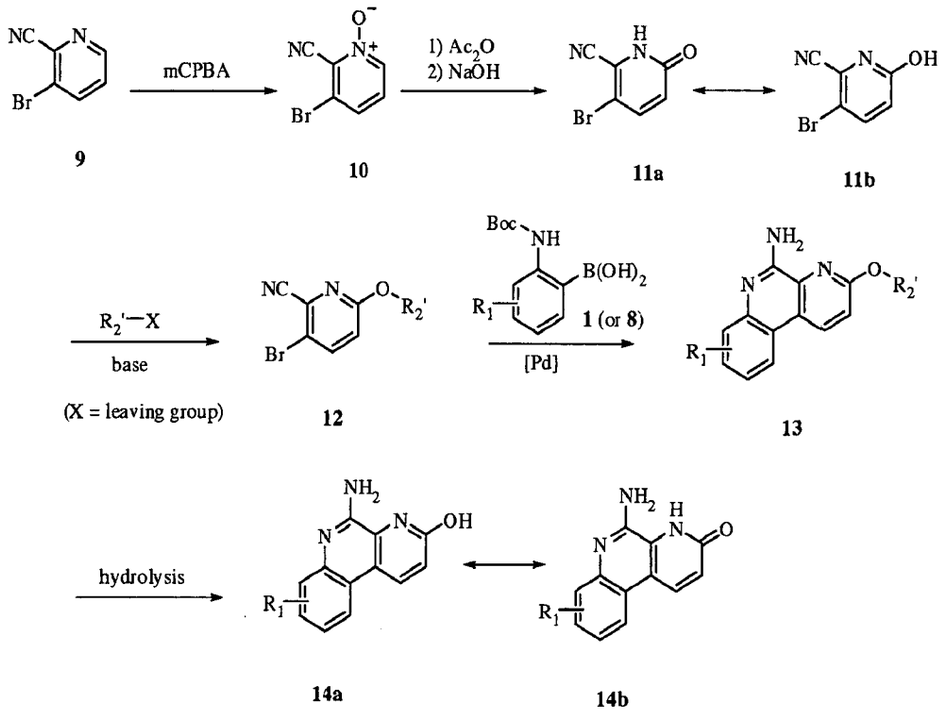


[000164] In certain embodiments, substituted or unsubsubstituted 2-bromoanilines used in scheme (III) were synthesized from their corresponding substituted or unsubsubstituted nitrobenzene compounds as illustrated below:



[000165] In certain embodiments, compounds of Formula (I) having oxygen-linked substituents were synthesized using the methodologies described in scheme (IV).

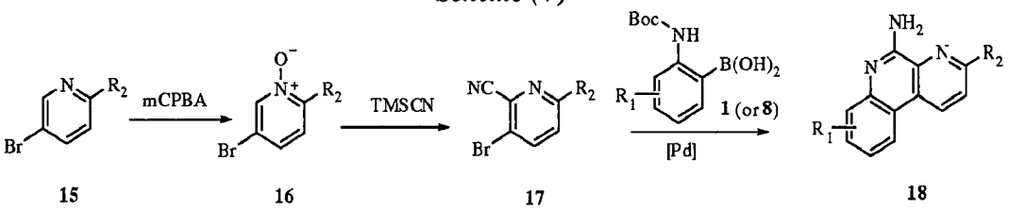
Scheme (IV)



[000166] In scheme (IV) benzonitrile (**9**) is first oxidized to N-oxide (**10**) with meta-chloroperbenzoic acid (mCPBA), and then converted into pyridone (**11**). Under specific basic conditions, the pyridone (**11**) is selectively alkylated on the oxygen to give the alkoxypicolinonitrile (**12**). Using palladium-mediated conditions, as in scheme (I), derivatives of alkoxypicolinonitrile (**12**) are coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give substituted or unsubstituted benzonaphthyridine (**13**) with oxygen-linked substituents. In certain embodiments, the benzonaphthyridine (**13**) with oxygen-linked substituents was hydrolyzed to obtain the corresponding benzonaphthyridone (**14**).

[000167] In other embodiments, compounds of Formula (I) having various substituents were synthesized using the methodologies described in scheme (V).

Scheme (V)

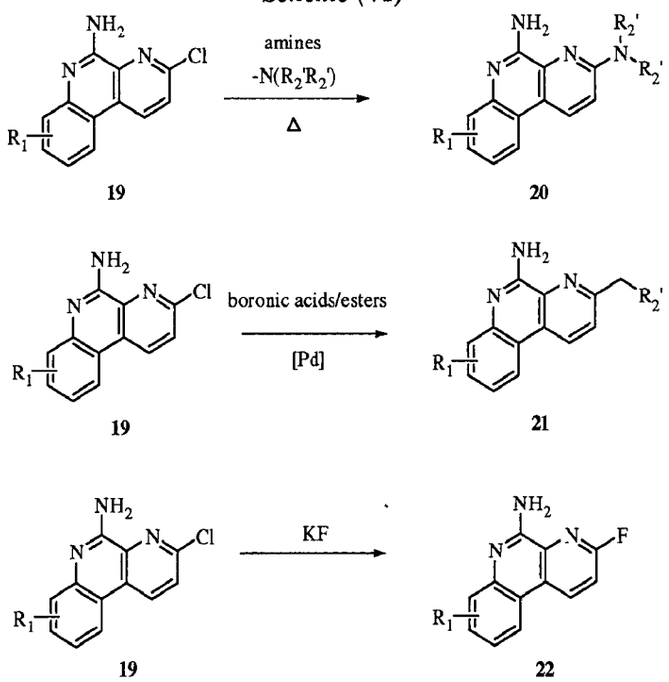


[000168] In scheme (V), 5-bromopyridines (**15**) substituted at the 2-position (shown as R_2 in scheme (V)) are first oxidized by meta-chloroperbenzoic acid (mCPBA) to give the N-oxide **16**,

which are then converted to the benzonitrile (**17**). Using palladium-mediated conditions, as in scheme (I), derivatives of benzonitrile (**17**) are coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give substituted or unsubstituted benzonaphthyridine (**18**) with various substituents in the 3-position. In other embodiments, benzonaphthyridine having various substituents in the 2-position are obtained by starting with 5-bromopyridines substituted at the 3-position.

[000169] In certain embodiments, the substituent in the 3-position of the benzonaphthyridine (**18**) is a chlorine atom, and this 3-chloro-benzonaphthyridine (**19**) is further modified to obtain other substituents at the 3-position of the benzonaphthyridines. Non-limiting examples of such modifications are illustrated in scheme (VI).

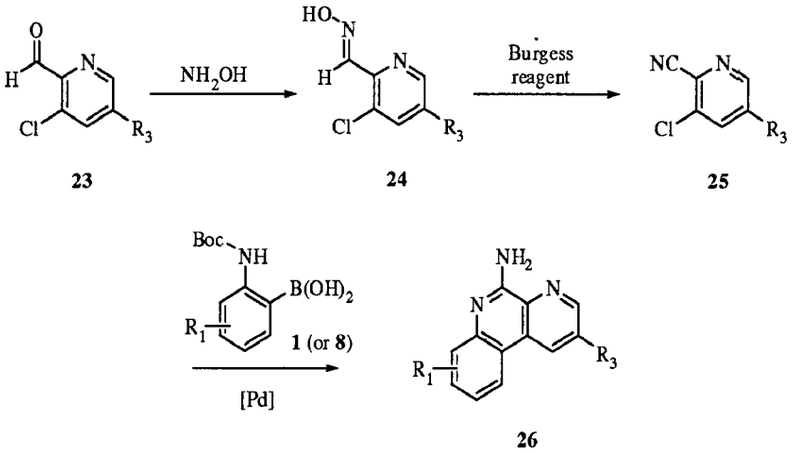
Scheme (VI)



[000170] In certain embodiments, as illustrated in scheme (VI), compounds of Formula (I) having N-linked substituents (derivatives of (**20**)) were obtained via S_NAr reactions by heating such chloro-derivatives (**19**) with various amines. In certain embodiments, as illustrated in scheme (VI), compounds of Formula (I) having carbon-linked substituents (derivatives of (**21**)) were obtained via Suzuki couplings using palladium-mediated conditions with various boronic acids or boronate esters. In certain embodiments, as illustrated in scheme (VI), compounds of Formula (I) were fluorinated by treatment of such chloro-derivatives (**19**) with potassium fluoride to give (3-fluorobenzo[f][1,7]-naphthyridin-5-amine (**22**)).

[000171] In other embodiments, compounds of Formula (I) having various substituents were synthesized using the methodologies described in scheme (VII).

Scheme (VII)

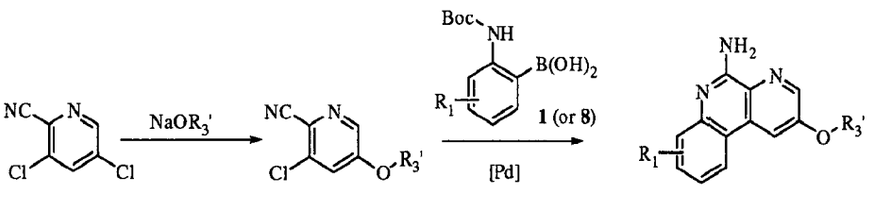


23 24 25 26

[000172] In scheme (VII), 3-chlorobenzaldehyde (**23**) (with a substituent R_3 at the 5-position) is first converted to the corresponding hydroxylamine (**24**), which is then used to make the corresponding nitrile (**25**). Using palladium-mediated conditions, as in scheme (I), derivatives of nitrile (**25**) are coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give the benzonaphthyridine (**26**) with various substituents in the 2-position.

[000173] In other embodiments, certain compounds of Formula (I) having oxygen-linked substituents were synthesized using the methodologies described in scheme (VIII).

Scheme (VIII)



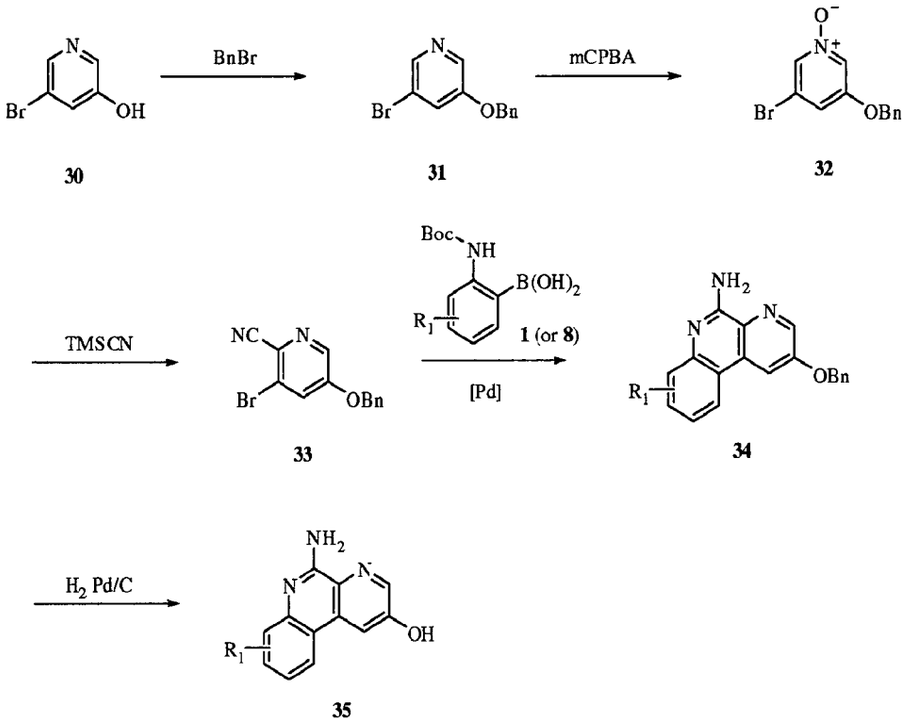
27 28 29

[000174] In scheme (VIII), benzonaphthyridines with various different oxygen-linked R_3 substituents at the 2-position are prepared using a 3,5-dihalopicolinonitrile, such as, by way of example only, 3,5-dichloropicolinonitrile (**27**), which is first mono-substituted with an alkoxy appendage to give the corresponding picolinonitrile (**28**). Then, using palladium-mediated conditions as in scheme (I), derivatives of nitrile (**27**) are coupled with substituted or unsubstituted

boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give the benzonaphthyridine (**29**) with various oxygen –linked substituents in the 2-position.

[000175] In certain embodiments, compounds of Formula (I) having hydroxy substituents, including benzonaphthyridines hydroxy substituents at the 2-position, were prepared using the synthetic route shown in scheme (IX).

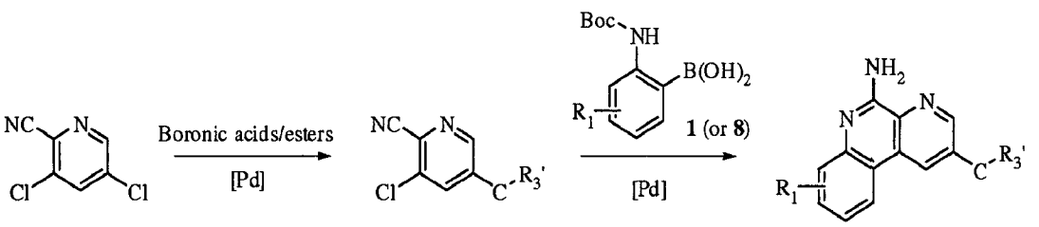
Scheme (IX)



[000176] In scheme (IX), a 5-halopyridin-3-ol such as, by way of example only, 3,5-bromopyridin-3-ol (**30**), is benzyl-protected at the hydroxyl group to give (**31**), which is then converted to the corresponding N-oxide (**32**). The N-oxide (**32**) is further converted into the nitrile (**33**). Then, using palladium-mediated conditions as in scheme (I), derivatives of nitrile (**33**) are coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give the benzonaphthyridine (**34**) which upon hydrogenation gives the benzonaphthyridine (**35**) with a hydroxyl substituent in the 2-position.

[000177] In other embodiments, certain compounds of Formula (I) having carbon-linked substituents, including benzonaphthyridines with various carbon-linked substituents at the 2-position, were prepared using the synthetic route shown in scheme (X).

Scheme (X)

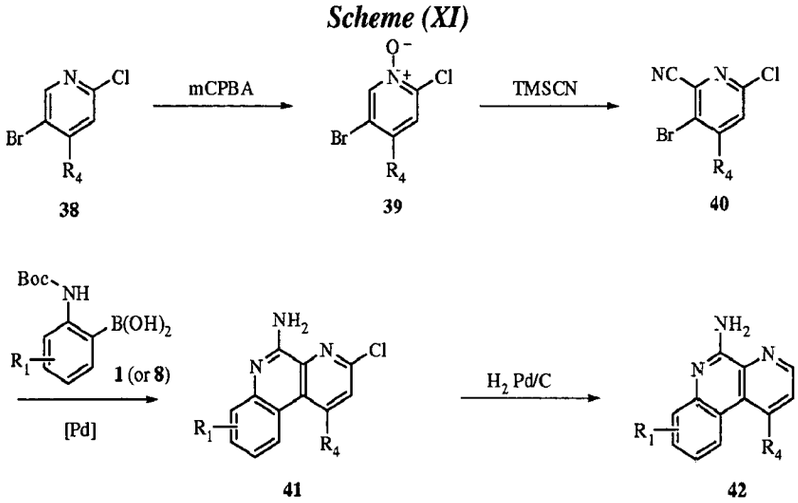


27 36 37

[000178] In scheme (X), a 3,5-dihalopicolinonitrile, such as, by way of example only, 3,5-dichloropicolinonitrile (**27**), is first mono-substituted using one equivalent of boronic acid/ester thereby giving the corresponding picolinonitrile (**36**). Using more vigorous palladium-mediated conditions as in scheme (I), derivatives of nitrile (**36**) are coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give the benzonaphthyridine (**37**) having carbon-linked substituents at the 2-position. In certain embodiments the carbon-linked substituent is an alkene, while in other embodiments such alkenes are further modified by hydrogenation to give benzonaphthyridines with alkyl groups at the 2-position.

[000179] In other embodiments, certain compounds of Formula (I) having various substituents, including benzonaphthyridines with various substituents at the 1-position, were synthesized using the methodologies described in scheme (XI).

Scheme (XI)



38 39 40

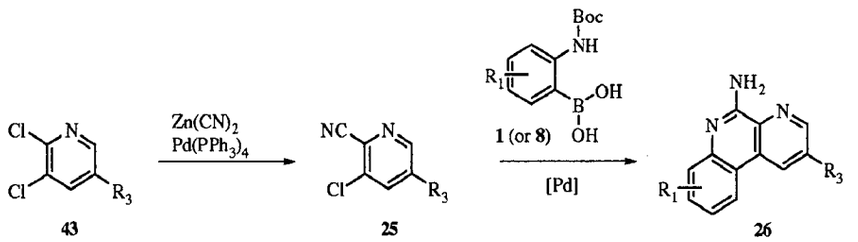
41 42

[000180] In scheme (XI), a 2,5-dihalopyridine substituted at the 4 position such as, by way of example only, 5-bromo-2-chloropyridine (**38**) is first converted to the corresponding N-oxide (**39**), which is then converted to the corresponding nitrile (**40**). Using palladium-mediated conditions as in scheme (I), derivatives of nitrile (**40**) are coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give the benzonaphthyridine (**41**) having

substituents at the 1-position. In certain embodiments, benzonaphthyridine (**41**) is further de-chlorinated to give benzonaphthyridine (**42**).

[000181] In other embodiments, certain compounds of Formula (I) having various substituents, including benzonaphthyridines with various substituents at the 2-position, were synthesized using the methodologies described in scheme (XII).

Scheme (XII)

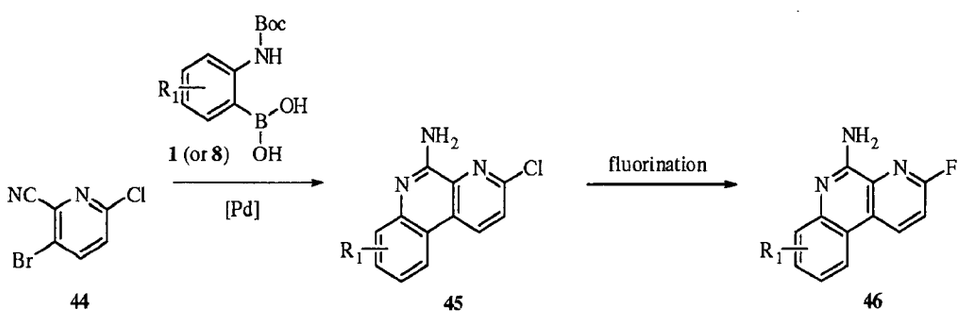


43 25 26

[000182] In scheme (XII), a 2,3-dihalopyridines substituted at the 5 position (**43**), such as, by way of example only, (5,6-dichloropyridin-3-yl)methanol, is first converted to the corresponding nitrile (**25**). Using palladium-mediated conditions as in scheme (I), derivatives of nitrile (**25**) are coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give the benzonaphthyridine (**26**) having substituents at the 2-position.

[000183] Various 3-halo naphthyridines were prepared according to the general methods as exemplified in Scheme XIII.

Scheme (XIII)



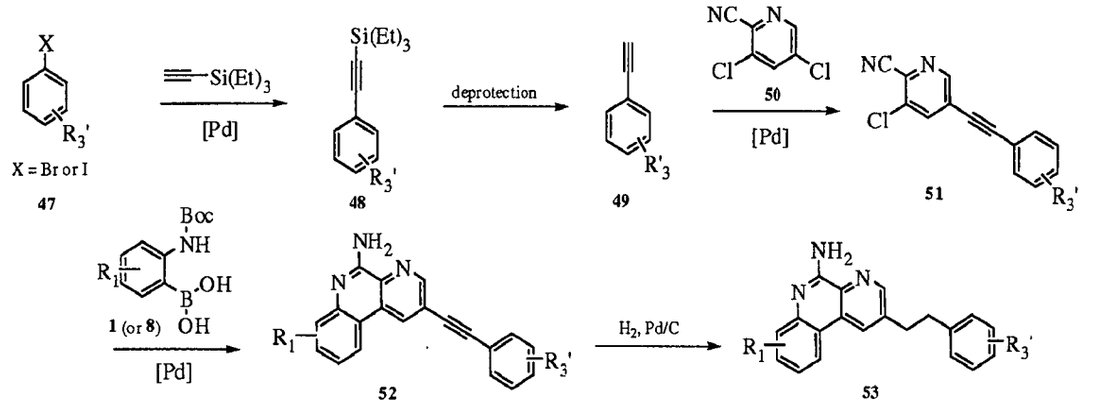
44 45 46

[000184] In scheme (XIII), using palladium-mediated conditions as in scheme (I), a 3,6-dihalo-2-cyanopyridines such as, by way of example only, 3-bromo-6-chloropicolinonitrile is coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give the benzonaphthyridine (**45**) having halogen substitutions at the 3-position. Further halogen exchange of benzonaphthyridine (**45**) gave benzonaphthyridine (**46**) with different halaogen substituents at the 3-position.

[000185] In other embodiments, certain compounds of Formula (I) were synthesized using the

methodologies described in scheme (XIV).

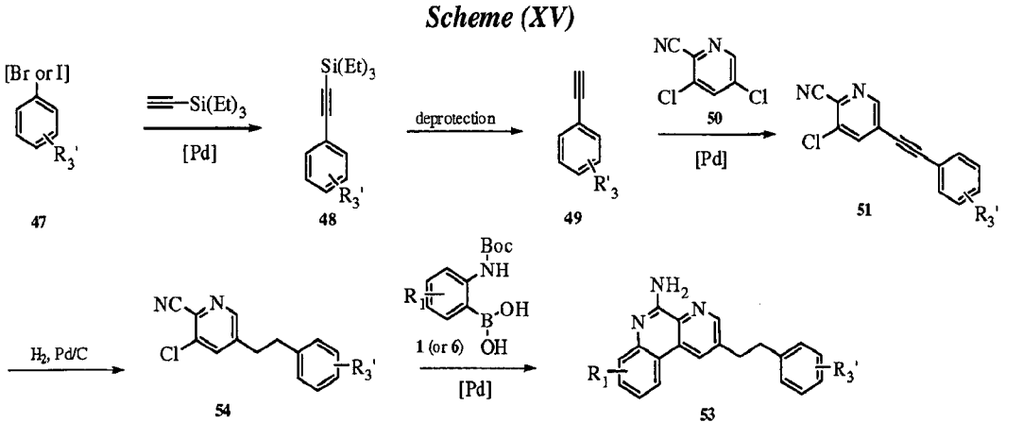
Scheme (XIV)



[000186] In scheme (XIV), aryl bromides or aryl iodides (**47**) substituted with various R_3' groups are coupled with triethyl(ethynyl)silane (or its equivalents) using palladium-mediated conditions to afford **48**. After deprotection of the silyl protection group, acetylene derivatives (**49**) are coupled with 3,5-dichloropicolinonitrile (**50**) using palladium-mediated conditions to afford 3-chloro-2-cyanopyridines (**51**). Derivatives of **51** such as, by way of example only, 3-chloro-5-(phenylethynyl)picolinonitrile is coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give the benzonaphthyridine (**52**). Compound **52** is then subjected under hydrogenation conditions to give benzonaphthyridines **53** with different substitutents at the R_3' position.

[000187] In other embodiments, certain compounds of Formula (I) were synthesized using the methodologies described in scheme (XV).

Scheme (XV)

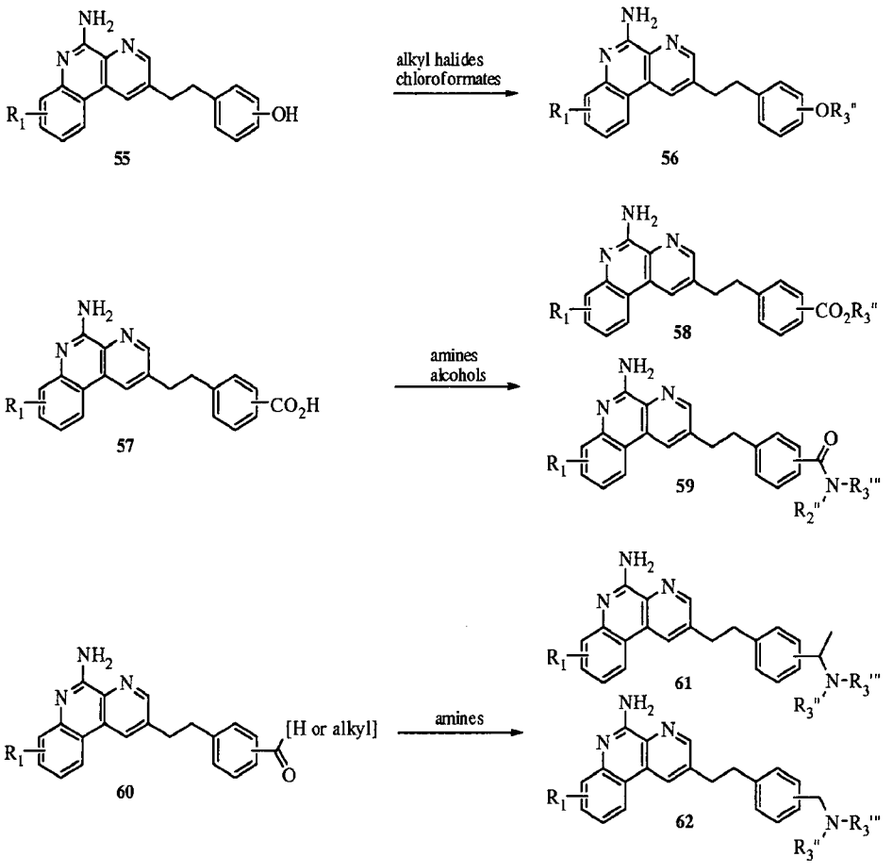


[000188] In scheme (XV), aryl bromides or aryl iodides (**47**) substituted with various R_3' groups are coupled with triethyl(ethynyl)silane (or its equivalents) using palladium-mediated conditions to

afford **48**. After deprotection of the silyl protection group, acetylene derivatives (**49**) are coupled with 3,5-dichloropicolinonitrile (**50**) using palladium-mediated conditions to afford 3-chloro-2-cyanopyridines (**51**). Derivatives of **51** such as, by way of example only, 3-chloro-5-(phenylethynyl)picolinonitrile is reduced to the corresponding 3-chloro-5-phenethylpicolinonitrile (**54**) under hydrogenation conditions. Compound **54** is coupled with substituted or unsubstituted boronic acids (**1**) (or substituted or unsubstituted boronate esters (**8**) to give benzonaphthyridines **53** with different substitutents at the R_3' position.

[000189] Benzonaphthyridines with various substitutions can be further converted into other functional groups using standard organic transformations. In certain embodiments, certain compounds of Formula (I) were synthesized using the methodologies described in scheme (XVI).

Scheme (XVI)

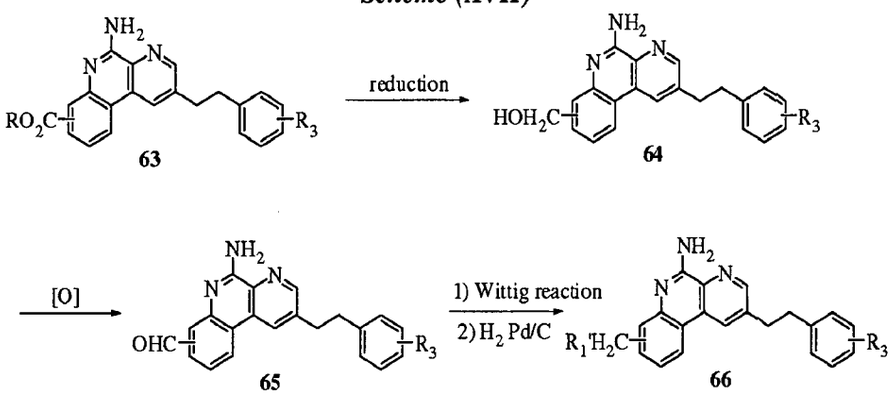


[000190] By way of example, in Scheme (XVI), benzonaphthyridines bearing a hydroxyl group (**55**) are converted to the corresponding ethers or carbonates (**56**). For example, benzonaphthyridines bearing a carboxylic acid group (**57**) are converted to the corresponding esters (**58**) or amides (**59**). For example, benzonaphthyridines bearing an aldehyde or ketone group (**60**) are converted to the corresponding amines (**61** or **62**). These benzonaphthyridines can

be further modified using the standard organic transformations.

[000191] In certain embodiments, certain compounds of Formula (I) were synthesized using the methodologies described in scheme (XVII).

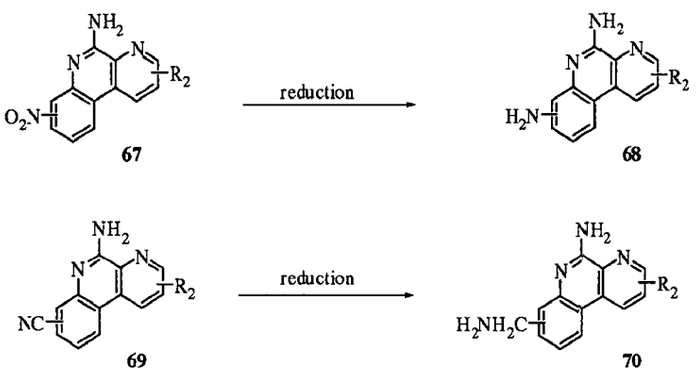
Scheme (XVII)



[000192] In scheme (XVII), benzonaphthyridines with various substitutions are further converted to different functional groups through standard organic transformations. For example, benzonaphthyridines bearing an ester group (**63**) are converted to the corresponding alcohol (**64**) by reduction using standard reducing agents. Compound **64** is oxidized to the corresponding aldehyde (**65**), which is further alkylated by a Wittig reaction followed by hydrogenation to give derivatives **66**. These benzonaphthyridines can be further modified using the standard organic transformations.

[000193] In certain embodiments, certain compounds of Formula (I) were synthesized using the methodologies described in scheme (XVIII).

Scheme (XVIII)

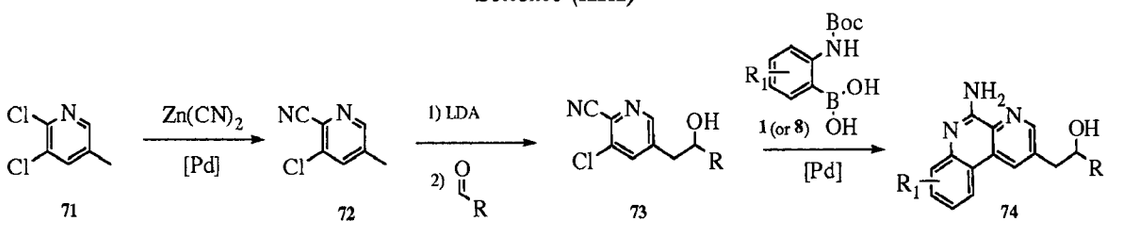


[000194] In scheme (XVIII), benzonaphthyridines with various substitutions are further converted to different functional groups through standard organic transformations. For example, benzonaphthyridines bearing a nitro group (**67**) or a cyano group (**69**) are converted to the corresponding amine (**68**) or methyl amine (**70**) by reduction using standard reducing agents.

These benzonaphthyridines can be further modified using the standard organic transformations.

[000195] In certain embodiments, certain compounds of Formula (I) were synthesized using the methodologies described in scheme (XIX).

Scheme (XIX)



[000196] In scheme (XIX), 2,3-dichloro-5-methylpyridine (**71**) is converted to the corresponding nitrile (**72**). Alcohol **73** is formed under Aldol condensation conditions, wherein compound **72** reacts with an aldehyde or ketone. Derivatives of **73** are then coupled with boronic acids (**1**) or boronate esters (**8**) to give the benzonaphthyridine (**74**).

[000197] The following examples are offered to illustrate, but not to limit, the compounds of Formula (I) provided herein, and the preparation of such compounds.

Pharmacology and Utility

[000198] When a foreign antigen challenges the immune system it responds by launching a protective response that is characterized by the coordinated interaction of both the innate and acquired immune systems. These two interdependent systems fulfill two mutually exclusive requirements: speed (contributed by the innate system) and specificity (contributed by the adaptive system).

[000199] The innate immune system serves as the first line of defense against invading pathogens, holding the pathogen in check while the adaptive responses are matured. It is triggered within minutes of infection in an antigen-independent fashion, responding to broadly conserved patterns in the pathogens (though it is not non-specific, and can distinguish between self and pathogens). Crucially, it also generates the inflammatory and co-stimulatory milieu (sometimes referred to as the danger signal) that potentiates the adaptive immune system and steers (or polarizes it) towards the cellular or humoral responses most appropriate for combating the infectious agent. The development of TLR modulators for therapeutic targeting of innate immunity has been reviewed (see Nature Medicine, 2007, 13, 552-559; Drug Discovery Today: Therapeutic Stategies, 2006, 3, 343-352 and Journal of Immunology, 2005, 174, 1259-1268).

[000200] The adaptive response becomes effective over days or weeks, but ultimately provides the fine antigenic specificity required for complete elimination of the pathogen and the generation

of immunologic memory. It is mediated principally by T and B cells that have undergone germline gene rearrangement and are characterized by specificity and long-lasting memory. However, it also involves the recruitment of elements of the innate immune system, including professional phagocytes (macrophages, neutrophils etc.) and granulocytes (basophils, eosinophils etc.) that engulf bacteria and even relatively large protozoal parasites. Once an adaptive immune response has matured, subsequent exposure to the pathogen results in its rapid elimination due to highly specific memory cells have been generated that are rapidly activated upon subsequent exposure to their cognate antigen.

[000201] Autoimmune diseases, are defined by (i) humoral or autoantibody response to a self antigen (by way of example only, Graves' primary hyperthyroidism with antibodies to the TSH receptor), or (ii) cellular response wherein immune cells destroy nonimmune cells from which the self-antigen is derived (by way of example only, the thyrocyte (Hashimoto's thyroiditis) or pancreatic β-islet cell (Type 1 diabetes). Many autoimmune diseases are a combination of both phenomena, for instance, Hashimoto's and Type 1 diabetes also have auto-antibodies, anti-thyroid peroxidase (TPO) or anti-glutamic acid decarboxylase (GAD)/Islet Cell. Autoimmune diseases often have an inflammatory component including, but not limited to, increases in adhesion molecules (by way of example only, vascular cell adhesion molecule-1 (VCAM-1), and altered leukocyte adhesion to the vasculature such as, by way of example only, colitis, systemic lupus, systemic sclerosis, and the vascular complications of diabetes.

[000202] Toll-like receptors (TLRs) are type-I transmembrane proteins characterized by an extracellular N-terminal leucine-rich repeat (LRR) domain, followed by a cysteine-rich region, a TM domain, and an intracellular (cytoplasmic) tail that contains a conserved region named the Toll/IL-1 receptor (TIR) domain. TLRs are pattern recognition receptors (PRR) that are expressed predominantly on immune cells including, but not limited to, dendritic cells, T lymphocytes, macrophages, monocytes and natural killer cells. The LLR domain is important for ligand binding and associated signaling and is a common feature of PRRs. The TIR domain is important in protein-protein interactions and is associated with innate immunity. The TIR domain also unites a larger IL-1 R/TLR superfamily that is composed of three subgroups. Members of the first group possess immunoglobin domains in their extracellular regions and include IL-1 and IL-18 receptors and accessory proteins as well as ST2. The second group encompasses the TLRs. The third group includes intracellular adaptor proteins important for signaling.

[000203] TLRs are a group of pattern recognition receptors which bind to pathogen-associated

molecular patterns (PAMPS) from bacteria, fungi, protozoa and viruses, and act as a first line of defense against invading pathogens. TLRs are essential to induce expression of genes involved in inflammatory responses, and TLRs and the innate immune system are a critical step in the development of antigen-specific acquired immunity.

[000204] Adaptive (humoral or cell-mediated) immunity is associated with the TLR signal mechanism of innate immunity. Innate immunity is a protective immune cell response that functions rapidly to fight environmental insults including, but not limited to, bacterial or viral agents. Adaptive immunity is a slower response, which involves differentiation and activation of naive T lymphocytes into T helper 1 (Th1) or T helper 2 (Th2) cell types. Th1 cells mainly promote cellular immunity, whereas Th2 cells mainly promote humoral immunity. Though primarily a host protective system, pathologic expression of the innate immunity signals emanating from the TLR pathway are implicated in initiating autoimmune-inflammatory diseases.

[000205] All TLRs appear to function as either a homodimer or heterodimer in the recognition of a specific, or set of specific, molecular determinants present on pathogenic organisms including bacterial cell-surface lipopolysaccharides, lipoproteins, bacterial flagellin, DNA from both bacteria and viruses and viral RNA. The cellular response to TLR activation involves activation of one or more transcription factors, leading to the production and secretion of cytokines and co-stimulatory molecules such as interferons, TNF-, interleukins, MIP-1 and MCP-1 which contribute to the killing and clearance of the pathogenic invasion.

[000206] TLR spatial expression is coincident with the host's environmental interface. While only a few other Toll-like proteins have been cloned in *Drosophila*, the human TLR family is composed of at least 11 members, TLR1 through TLR11, that elicit overlapping yet distinct biological responses due to differences in cellular expression and signaling pathways they initiate. Each of the TLRs is expressed on a different subset of leukocytes and each of the TLRs is specific in its expression patterns and PAMP sensitivities and detects different subsets of pathogens allowing vigilant surveillance by the immune system.

Toll-like Receptor 1 (TLR1)

[000207] TLR1 maps to chromosome 4p14 and its sequence encodes a putative 786 amino acid (aa) protein with 18 N-terminal LRRs and a calculated molecular weight of 84 kDa. TLR1 is most closely related to TLR6 and TLR10 with 68% and 48% overall (aa) sequence identity, respectively.

[000208] TLR1 mRNA is ubiquitously expressed and found at higher levels than the other TLRs. Of the major leukocyte populations, TLR1 is most highly expressed by monocytes, but is also

expressed by macrophages, dendritic cells, polymorphonuclear leukocytes, B, T, and NK cells. *In vivo*, two different sized transcripts for TLR1 are observed suggesting that the mRNA is alternatively spliced to generate two different forms of the protein. *In vitro*, TLR1 mRNA and protein expression is upregulated in monocytic leukemic (THP-1) cells upon PMA-induced differentiation. TLR1 expression is upregulated by autocrine IL-6, and is also elevated by IFN-γß, IL-10, and TNF-α. However, TLR1 level is unaffected by exposure to both Gram-positive and Gram-negative bacteria. *Ex vivo*, both monocyte and granulocyte TLR1 expression is downregulated after exposure to Gram-negative bacteria. TLR1 forms a heterodimer with TLR2. TLR1 also heterodimerizes with TLR4, which inhibits TLR4 activity.

Toll-like Receptor 2 (TLR2)

[000209] TLR2 maps to chromosome 4q31-32 and encodes a putative 784 (aa) protein with 19 N-terminal LLRs and a calculated molecular weight of 84 kDa. TLR2 is most closely related to TLR6 with 31% overall (aa) sequence identity.

[000210] TLR2 mRNA expression is observed in brain, heart, lung, and spleen tissues and is highest in PBLs, specifically those of myelomonocytic origin. *In vivo*, two different sized transcripts for TLR2 are observed suggesting that the mRNA is alternatively spliced. *In vitro*, TLR2 mRNA and protein expression is upregulated in monocytic leukemic (THP-1) cells upon PMA-induced differentiation. TLR2 is upregulated by autocrine IL-6 and TNF-α, IL-1β, and IL-10. TLR2 mRNA expression is elevated after exposure to both Gram-positive and Gram-negative bacteria. TLR2 forms heterodimers with TLR1, TLR6, and possibly TLR10, where each complex is particularly sensitive to subsets of TLR2-associated PAMPs. TLR2 complexes recognize a wide range of PAMPs, mostly from bacteria. These include, but are not limited to, lipoarabinomannan (LAM), lipopolysaccharide (LPS), lipoteichoic acid (LTA), peptidoglycan (PGN), and other glycolipids, glycoproteins, and lipoproteins. TLR2 complexes are also capable of detecting viruses, including but not limited to, measles virus (MV), human cytomegalovirus (HCMV), and hepatitis C virus (HCV) and fungal PAMPs, including but not limited to, zymosan. TLR2 recognizes a variety of lipoproteins/lipopeptides from various pathogens such as, by way of example only, Gram-positive bacteria, mycobacteria, Trypanosoma cruzi, fungi and Treponema. In addition, TLR2 recognizes LPS preparations from non-enterobacteria such as, by way of example only, Leptospira interrogans, Porphyromonas gingivalis and Helicobacter pylori. TLR2 complexes are capable of both detection of non-self patterns and detecting altered self patterns, such as those displayed by necrotic cells. TLR2 is recruited to phagosomes and is involved in the internalization of microbial products by cells.

Toll-like Receptor 3 (TLR3)

[000211] TLR3 maps to chromosome 4q35 and its sequence encodes a putative 904 (aa) protein with 24 N-terminal LRRs and a calculated molecular weight of 97 kDa. TLR3 is most closely related to TLR5, TLR7, and TLR8, each with 26% overall (aa) sequence identity.

[000212] TLR3 mRNA is expressed at highest levels in the placenta and pancreas. TLR3 is expressed by dendritic cells, T and NK cells. *In vivo*, two different sized transcripts for TLR3 are observed suggesting that the mRNA is alternatively spliced to generate two different forms of the protein. *In vitro*, PMA-differentiated THP-1 TLR3 is moderately upregulated by autocrine IFN-γ, IL-1ß, IL-6, IL-10, and TNF-α. TLR3 mRNA is elevated after exposure to Gram-negative bacteria and to an even greater extent in response to Gram-positive bacteria. *Ex vivo*, TLR3 expression is elevated in both monocytes and granulocytes upon exposure to Gram-negative bacteria. TLR3 forms a homodimer and recognizes viral double stranded RNA (dsRNA). While it is generally assumed that TLRs are expressed on the cell surface, however those TLRs sensitive to internal PAMPs, such as dsRNA in the case of TLR3, are localized intracellularly in the lysosomal compartment.

Toll-like Receptor 4 (TLR4)

[000213] TLR4 maps to chromosome 9q32-33, and shows a high degree of similarity to dToll over the entire (aa) sequence. The TLR4 sequence encodes an 839 (aa) protein with 22 N-terminal LRR regions and a calculated molecular weight of 90 kDa. TLR4 is most closely related to TLR1 and TLR6 each with 25% overall (aa) sequence identity.

[000214] *In vivo*, TLR4 mRNA is expressed as a single transcript, and found at highest levels in spleen and PBLs. Of the PBL populations, TLR4 is expressed by B cells, dendritic cells, monocytes, macrophages, granulocytes, and T cells. TLR4 is also expressed in myelomonocytic cells and is highest in mononuclear cells. *In vitro*, TLR4 mRNA and protein expression is upregulated in THP-1 cells upon PMA-induced differentiation. TLR4 is moderately upregulated by autocrine IFN-γ, IL-1β. TLR4 mRNA expression in THP-1 cells is unaffected by exposure to both Gram-positive and Gram-negative bacteria. *Ex vivo*, granulocyte, and monocyte, TLR4 expression is upregulated upon exposure to Gram-negative bacteria.

[000215] TLR4 forms a homodimer and requires the extracellular association of an additional component, MD-2. Although TLR2 complexes are capable of recognizing lipopolysaccharide (LPS), TLR4 is generally considered the LPS receptor. MD-2-associated TLR4 homodimers do not bind LPS directly, however. LPS must first be bound by the soluble LPS binding protein (LBP). LBP is then bound by either soluble or GPI-linked CD14. Additional cell type-dependent

components required for LPS detection by TLR4 include CXCR4, GDF-5, CD55, various heat shock proteins (HSPs), and complement receptors (CRs). The TLR4 complex also recognizes a few other bacterial PAMPs including LTA. Further, the TLR4 complex recognizes viruses including respiratory syncytial virus (RSV), hepatitis C virus (HCV), and mouse mammary tumor virus (MMTV). The TLR4 complex can also recognize endogenous ligands, for example, heat shock proteins (HSP60 and HSP70), fibrinogen, domain A of fibronectin, oligosaccharides of hyaluronic acid, heparan sulfate, surfactant protein A (SP-A), and β-defensins. TLR4 also forms heterodimers both with TLR5, which enhances its activity, and also with TLR1, which inhibits its activity.

Toll-like Receptor 5 (TLR5)

[000216] TLR5 maps to chromosome 1q41-42, and the gene encodes a putative 858 (aa) protein with a calculated molecular weight of 91 kDa. It is most closely related to TLR3 with 26% overall (aa) sequence identity.

[000217] *In vivo*, TLR5 mRNA is expressed as a single transcript in ovary, prostate, and PBLs. TLR5 is expressed by several PBL populations with the highest expression found in monocytes. TLR5 is also expressed on the basolateral side of intestinal epithelial cells and intestinal endothelial cells of the subepithelial compartment. *In vitro*, TLR5 is upregulated in PMA-differentiated THP-1 cells by autocrine IL-6, IL-10, and TNF-α, but is also elevated by IFN-γβ. TLR5 mRNA expression is elevated after exposure to both Gram-positive and Gram-negative bacteria. *Ex vivo*, granulocyte and monocyte TLR5 expression is downregulated upon exposure to Gram-negative bacteria. TLR5 forms a homodimer as well as a heterodimer with TLR4. Both complexes function to recognize the Flagellin protein of flagellated bacteria. Expression of human TLR5 in CHO cells confers response to flagellin, a monomeric constituent of bacterial flagella. Flagellin activates lung epithelial cells to induce inflammatory cytokine production. A stop codon polymorphism in TLR5 has been associated with susceptibility to pneumonia caused by the flagellated bacterium Legionella pneumophila.

Toll-like Receptor 6 (TLR6)

[000218] TLR6 maps to chromosome 4p14, and the TLR6 sequence encodes a 796 (aa) protein containing 20 N-terminal LRR motifs with a calculated molecular weight of 91 kDa. TLR6 is most closely related to TLR1, TLR10, and TLR2 with 68%, 46%, and 31% overall (aa) sequence identity, respectively.

[000219] *In vivo*, TLR6 transcript is observed in thymus, spleen, and lung. TLR6 mRNA expression is highest in B cells and monocytes. *In vitro*, TLR6 mRNA expression is upregulated in

THP-1 cells upon PMA-induced differentiation. TLR6 is moderately upregulated by autocrine IFN-γ, IL-1β. However, TLR6 mRNA expression in THP-1 cells is unaffected by exposure to both Gram-positive and Gram-negative bacteria. *Ex vivo*, monocyte andgranulocyte TLR6 expression is downregulated upon exposure to Gram-negative bacteria. TLR6 forms a heterodimer with TLR2. Like TLR1, TLR6 is thought to specify or enhance the PAMP sensitivity of TLR2 and contribute to its signaling capabilities through heterodimerization.

Toll-like Receptor 7 (TLR7)

[000220] TLR7 maps to human chromosome Xp22, and the TLR7 sequence encodes a 1049 (aa) protein containing 27 N-terminal LRRs with a calculated molecular weight of 121 kDa. TLR7 is most closely related to TLR8 and TLR9 with 43% and 36% overall (aa) sequence identity, respectively.

[000221] *In vivo*, TLR7 mRNA is expressed in lung, placenta, spleen, lymph node, and tonsil. TLR7 mRNA expression is highest in monocytes, B cells, and plasmocytoid dendritic cells. *In vitro*, TLR7 mRNA expression is upregulated in THP-1 cells upon PMA-induced differentiation. TLR7 is highly upregulated by exposure to IL-6 and to a slightly lesser extent by autocrine IFN-γ, IL-1β. TLR7 mRNA expression in THP-1 cells is elevated after exposure to both Gram-positive and Gram-negative bacteria. *Ex vivo*, expression of TLR7 is elevated after exposure to both Gram-positive and Gram-negative bacteria in monocytes and to a greater degree in granulocytes. TLR7 is expressed in the endosome. The role of TLR7, is to detect the presence of "foreign" single-stranded RNA within a cell, as a means to respond to viral invasion. TLR7 is a structurally highly conserved protein which recognizes guanosine- or uridine-rich, single-stranded RNA (ssRNA) from viruses such as human immunodeficiency virus, vesicular stomatitis virus and influenza virus

Toll-like Receptor 8 (TLR8)

[000222] TLR8 maps to chromosome Xp22, and the TLR8 sequence encodes a 1041 (aa) protein containing 26 N-terminal LRRs with a calculated molecular weight of 120 kDa. TLR8 is most closely related to TLR7 and TLR9 with 43% and 35% overall (aa) sequence identity, respectively.

[000223] *In vivo*, TLR8 mRNA is expressed in lung, placenta, spleen, lymph node, bone marrow, and PBLs, with highest expression found in cells of myeloid origin, such as monocytes, granulocytes and myeloid dendritic cells. *In vitro*, TLR8 mRNA expression is upregulated in THP-1 cells upon PMA-induced differentiation. TLR8 is highly upregulated by autocrine IL-1β, IL-6, IL-10, and TNF-α, and is even more enhanced by exposure to IFN-γ. TLR8 mRNA expression in THP-1 cells is elevated after exposure to both Gram-positive and Gram-negative bacteria. *Ex vivo*, monocyte TLR8 expression increases while granulocyte expression decreases on exposure to

Gram-negative bacteria. TLR8 is expressed in the endosome. The role of TLR8 is to detect the presence of "foreign" single-stranded RNA within a cell, as a means to respond to viral invasion. TLR8 is a structurally highly conserved protein which recognizes guanosine- or uridine-rich, single-stranded RNA (ssRNA) from viruses such as human immunodeficiency virus, vesicular stomatitis virus and influenza virus.

Toll-like Receptor 9 (TLR9)

[000224] TLR9 maps to chromosome 3p21, and the TLR9 sequence encodes a 1032 (aa) protein containing 27 N-terminal LRRs with a calculated molecular weight of 116 kDa. TLR9 is most closely related to TLR7 and TLR8 with 36% and 35% overall (aa) sequence identity, respectively.

[000225] *In vivo*, TLR9 mRNA is expressed in spleen, lymph node, bone marrow, and PBLs. Specifically, TLR9 mRNA is expressed at the highest levels in B cells and dendritic cells. *In vitro*, TLR9 is moderately upregulated by autocrine IFN-γ, IL-1ß, IL-6, IL-10, and TNF-α in PMA-differentiated THP-1 cells. TLR9 mRNA expression in THP-1 cells is unaffected by exposure to both Gram-positive and Gram-negative bacteria. *Ex vivo*, TLR9 expression in monocytes and particularly in granulocytes is downregulated in response to Gram-negative bacteria. TLR9 forms a homodimer and recognizes unmethylated bacterial DNA. TLR9 is involved in the inflammatory response to bacterial DNA and oligonucleotides that contain unmethylated CpG DNA sequences. TLR9 is localized internally, perhaps in lysosomic or endocytic compartments where it would more likely encounter PAMPs including unmethylated CpG DNA sequences.

[000226] TLR9 is a receptor for CpG DNA, and recognizes bacterial and viral CpG DNA. Bacterial and viral DNA contains unmethylated CpG motifs, which confer its immunostimulatory activity. In vertebrates, the frequency of CpG motifs is severely reduced and the cytosine residues of CpG motifs are highly methylated, leading to abrogation of the immunostimulatory activity. Structurally, there are at least two types of CpG DNA: B/K-type CpG DNA is a potent inducer of inflammatory cytokines such as IL-12 and TNF-α; A/D-type CpG DNA has a greater ability to induce IFN-α production from plasmacytoid dendritic cells (PDC). TLR9 is also involved in pathogenesis of autoimmune disorders, and may be important in Graves' autoimmune hyperthyroidism and production of rheumatoid factor by auto-reactive B cells. Similarly, internalization by the Fc receptor can cause TLR9 mediated PDC induction of IFN-α by immune complexes containing IgG and chromatin, which are implicated in the pathogenesis of systemic lupus erythematosus (SLE). TLR9 is involved in the pathogenesis of several autoimmune diseases through recognition of the chromatin structure.

Toll-like Receptor 10 (TLR10)

[000227] The TLR10 sequence encodes a putative 811 (aa) protein with molecular weight of 95 kDa. TLR10 is most closely related to TLR1 and TLR6 with 48% and 46% overall (aa) identity, respectively.

[000228] *In vivo*, TLR10 mRNA expression is highest in immune system-related tissues including spleen, lymph node, thymus, and tonsil. TLR10 mRNA is most highly expressed on B cells and plasmacytoid dendritic cells (PDCs). *In vitro*, TLR10 is moderately upregulated by autocrine IFN-γ, IL-1β, IL-6, IL-10, and TNF-α in PMA-differentiated THP-1 cells. TLR10 mRNA expression in THP-1 cells is elevated after exposure to both Gram-positive and Gram-negative bacteria. *Ex vivo*, monocyte TLR10 expression increases, while granulocyte expression decreases on exposure to Gram-negative bacteria.

Toll-like Receptor 11 (TLR11)

[000229] TLR11 is expressed in bladder epithelial cells and mediate resistance to infection by uropathogenic bacteria in mouse.

[000230] As presented above, TLR2 and TLR4 recognize Gram-positive and Gram-negative bacterial cell wall products, respectively; TLR5 recognizes a structural epitope of bacterial flagellin; TLR3, TLR7, TLR8, and TLR9 recognize different forms of microbial-derived nucleic acid.

[000231] The TIR domains interact with several TIR domain-containing adaptor molecules (MyD88), TIR domain-containing adaptor protein (TIRAP), TIR domain-containing adaptor-inducing IFN-β (TRIF), and TRIF-related adaptor molecule (TRAM) which activate a cascade of events resulting in transcription factor induction.

TLR Signaling Pathways.

[000232] TLRs are distributed throughout the cell. TLR1, TLR2, TLR3 and TLR4 are expressed on the cell surface, whereas, TLR3, TLR7, TLR8 and TLR9 are expressed in intracellular compartments such as endosomes. TLR3-, TLR7- or TLR9-mediated recognition of their ligands require endosomal maturation and processing. When macrophages, monocytes, dendritic cells or nonimmune cells that become antigen presenting cells engulf bacteria by phagocytosis, the bacteria degrade and CpG DNA is release into phagosomes-lysosomes or in endosomes-lysosomes wherein they can interact with TLR9 that has been recruited from the endoplasmic reticulum upon non-specific uptake of CpG DNA. Furthermore, when viruses invade cells by receptor-mediated endocytosis, the viral contents are exposed to the cytoplasm by fusion of the viral membrane with

the endosomal membrane. This results in exposure of TLR ligands such as dsRNA, ssRNA and CpG DNA to TLR9 in the phagosomal/lysosomal or endosomal/lysosomal compartments.

[000233] In the signaling pathways downstream of the TIR domain, a TIR domain-containing adaptor, MyD88, is essential for induction of inflammatory cytokines such as TNF-α and IL-12 through all TLRs. Although TIR domain-containing adaptor molecules (MyD88) are common to all TLRs, individual TLR signaling pathways are divergent and activation of specific TLRs leads to slightly different patterns of gene expression profiles. By way of example only, activation of TLR3 and TLR4 signaling pathways results in induction of type I interferons (IFNs), while activation of TLR2-and TLR5-mediated pathways do not. However, activation of TLR7, TLR8 and TLR9 signaling pathways also leads to induction of Type I IFNs, although this occurs through mechanisms distinct from TLR3/4-mediated induction.

[000234] Once engaged, TLRs initiate a signal transduction cascade leading to activation of NFκB via the adapter protein myeloid differentiation primary response gene 88 (MyD88) and recruitment of the IL-1 receptor associated kinase (IRAK). The MyD88-dependent pathway is analogous to signaling by the IL-1 receptors, and it is regarded that MyD88, harboring a C-terminal TIR domain and an N-terminal death domain, associates with the TIR domain of TLRs. Upon stimulation, MyD88 recruits IRAK-4 to TLRs through interaction of the death domains of both molecules, and facilitates IRAK-4-mediated phosphorylation of IRAK-1. Phosphorylation of IRAK-1 then leads to recruitment of TNF-receptor associated factor 6 (TRAF6), leading to the activation of two distinct signaling pathways. One pathway leads to activation of AP-1 transcription factors through activation of MAP kinases. Another pathway activates the TAK1/TAB complex, which enhances activity of the IκB kinase (IKK) complex. Once activated, the IKK complex induces phosphorylation and subsequent degradation of the NFκB inhibitor IκB, which leads to nuclear translocation of transcription factor NFκB and the initiation of transcription of genes whose promoters contain NFκB binding sites, such as cytokines. The MyD88-dependent pathway plays a crucial role and is essential for inflammatory cytokine production through all TLRs.

[000235] Stimulation of TLR8-expressing cells, such as PBMCs results in production of high levels of IL-12, IFN-γ, IL-1, TNF-α, IL-6 and other inflammatory cytokines. Similarly, stimulation of TLR7-expressing cells, such as plasmacytoid dendritic cells, results in production of high levels of interferon-α (IFNα) and low levels of inflammatory cytokines. Thus, through activation of dendritic cells and other antigen-presenting cells, TLR7, TLR8 or TLR9 engagement

and cytokine production is expected to activate diverse innate and acquired immune response mechanisms leading to the destruction of pathogens, infected cells or tumor cells.

[000236] Compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are useful as modulators of toll-like receptor activity, and are used in the treatment of a wide variety of diseases and/or disorders associated with such receptors. In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are modulators of TLR7 activity and are useful in the treatment of diseases and/or disorders associated with TLR7. In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are agonists of TLR7 activity and are useful in the treatment of diseases and/or disorders associated with TLR7. In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are modulators of TLR8 activity and are useful in the treatment of diseases and/or disorders associated with TLR8. In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are agonists of TLR8 activity and are useful in the treatment of diseases and/or disorders associated with TLR8.

[000237] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of respiratory diseases and/or disorders including, but not limited to, asthma, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, exercise-induced asthma, drug-induced asthma (including aspirin and NSAID-induced) and dust-induced asthma, chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute

and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus.

[000238] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of dermatological disorders including, but not limited to, psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, basal cell carcinoma, actinic keratosis, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis;cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions.

[000239] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of ocular diseases and/or disorders including, but not limited to, blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune, degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial.

[000240] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of genitourinary diseases and/or disorders including, but not limited to, nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female).

[000241] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or

combinations provided herein are used in the treatment of allograft rejection including, but not limited to, acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease.

[000242] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of other auto-immune and allergic disorders including, but not limited to, rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, Crohns disease, inflammatory bowel disease (IBD), Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome and Sazary syndrome.

[000243] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are used in the treatment of cancer including, but not limited to, prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumor recurrences, and paraneoplastic syndromes. In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are useful as modulators of toll-like receptor activity, and are used in the treatment of neoplasias including, but not limited to, basal cell carcinoma, squamous cell carcinoma, actinic keratosis, melanoma, carcinomas, sarcomas, leukemias, renal cell carcinoma, Kaposi's sarcoma, myelogeous leukemia, chronic lymphocytic leukemia and multiple myeloma.

[000244] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of infectious diseases including, but not limited to, viral diseases such as genital warts, common warts, plantar warts, respiratory syncytial virus (RSV), hepatitis B, hepatitis C, Dengue virus, herpes simplex virus (by way of example only, HSV-I, HSV-II, CMV, or VZV), molluscum contagiosum, vaccinia, variola, lentivirus, human immunodeficiency virus (HIV), human papilloma virus (HPV), cytomegalovirus (CMV), varicella zoster virus (VZV), rhinovirus, enterovirus, adenovirus, coronavirus (e.g., SARS), influenza, para-

influenza, mumps virus, measles virus, papovavirus, hepadnavirus, flavivirus, retrovirus, arenavirus (by way of example only, LCM, Junin virus, Machupo virus, Guanarito virus and Lassa Fever) and filovirus (by way of example only, ebola virus or marbug virus).

[000245] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of bacterial, fungal, and protozoal infections including, but not limited to, tuberculosis and mycobacterium avium, leprosy; pneumocystis carnii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection, leishmaniasis, infections caused by bacteria of the genus *Escherichia, Enterobacter, Salmonella, Staphylococcus, Klebsiella, Proteus, Pseudomonas, Streptococcus, and Chlamydia*, and fungal infections such as *candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis.*

[000246] In certain embodiments, the compounds of Formula (I) and (I-A), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, are used as immune potentiators. In certain embodiments, the compounds provided herein are included in immunogenic compositions or are used in combination with immunogenic compositions. In certain embodiments, the immunogenic compositions are useful as vaccines, and the compound is present in an amount sufficient to enhance an immune response to the vaccine, or to an antigen admixed with the compound. The vaccine comprises at least one antigen, which may be an bacterial antigen or a cancer-associated antigen, or a viral antigen. In certain embodiments, the compounds of Formula (I) or (I-A), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are included in therapeutic vaccines or are used in combination with therapeutic vaccines. In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are included in prophylactic vaccines or used in combination with prophylactic vaccines. In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are included in, or are used in combination with, therapeutic viral vaccines. In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions provided herein are included in, or are used in combination with, with cancer vaccines.

[000247] In other embodiments, the compounds of Formula (I), or a pharmaceutically acceptable

salt or solvate thereof, described herein are useful for the treatment of damaged or ageing skin such as scarring and wrinkles.

Administration and Pharmaceutical Compositions

[000248] For the therapeutic uses of compounds of Formula (I), or pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, described herein, such compounds are administered in therapeutically effective amounts either alone or as part of a pharmaceutical composition. Accordingly, provided herein are pharmaceutical compositions, which comprise at least one compound of Formulas (I) described herein, pharmaceutically acceptable salts and/or solvates thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. In addition, such compounds and compositions are administered singly or in combination with one or more additional therapeutic agents. The method of administration of such compounds and compositions include, but are not limited to, oral administration, rectal administration, parenteral, intravenous administration, intravitreal administration, intramuscular administration, inhalation, intranasal administration, topical administration, ophthalmic administration or otic administration.

[000249] The therapeutically effective amount will vary depending on, among others, the disease indicated, the severity of the disease, the age and relative health of the subject, the potency of the compound administered, the mode of administration and the treatment desired. In certain embodiments, the daily dosage of a compound of Formula (I), satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5mg/kg per body weight. In certain embodiments, the daily dosage of a compound of Formula (I), administered by inhalation, is in the range from 0.05 micrograms per kilogram body weight (μg/kg) to 100 micrograms per kilogram body weight (μg/kg). In other embodiments, the daily dosage of a compound of Formula (I), administered orally, is in the range from 0.01 micrograms per kilogram body weight (μg/kg) to 100 milligrams per kilogram body weight (mg/kg). An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5mg to about 100mg of a compound of Formula (I), conveniently administered, e.g. in divided doses up to four times a day or in controlled release form. In certain embodiment, unit dosage forms for oral administration comprise from about 1 to 50 mg of a compound of Formula (I).

[000250] Other aspects provided herein are processes for the preparation of pharmaceutical composition which comprise at least one compound of Formulas (I) described herein, or pharmaceutically acceptable salts and/or solvates thereof. In certain embodiments, such processes include admixing a compound of the Formula (I) described herein, and pharmaceutically

acceptable salts and solvates thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients. In certain embodiments, the pharmaceutical compositions comprising a compound of Formula (I) in free form or in a pharmaceutically acceptable salt or solvate form, in association with at least one pharmaceutically acceptable carrier, diluent or excipient are manufactured by mixing, granulating and/or coating methods. In other embodiments, such compositions are optionally contain excipients, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In other embodiments, such compositions are sterilized.

Oral Dosage Forms

[000251] In certain embodiments, the pharmaceutical compositions containing at least one compound of Formula (I) are administered orally as discrete dosage forms, wherein such dosage forms include, but are not limited to, capsules, gelatin capsules, caplets, tablets, chewable tablets, powders, granules, syrups, flavored syrups, solutions or suspensions in aqueous or non-aqueous liquids, edible foams or whips, and oil-in-water liquid emulsions or water-in-oil liquid emulsions.

[000252] The capsules, gelatin capsules, caplets, tablets, chewable tablets, powders or granules, used for the oral administration of at least one compound of Formula (I) are prepared by admixing at least one compound of Formula (I) (active ingredient) together with at least one excipient using conventional pharmaceutical compounding techniques. Non-limiting examples of excipients used in oral dosage forms described herein include, but are not limited to, binders, fillers, disintegrants, lubricants, absorbents, colorants, flavors, preservatives and sweeteners.

[000253] Non-limiting examples of such binders include, but are not limited to, corn starch, potato starch, starch paste, pre-gelatinized starch, or other starches, sugars, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, tragacanth, guar gum, cellulose and its derivatives (by way of example only, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethylcellulose, methyl cellulose, hydroxypropyl methylcellulose and microcrystalline cellulose), magnesium aluminum silicate, polyvinyl pyrrolidone and combinations thereof.

[000254] Non-limiting examples of such fillers include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. In certain embodiments, the binder or filler in pharmaceutical compositions provided herein are present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage

form.

[000255] Non-limiting examples of such disintegrants include, but are not limited to, agar-agar, alginic acid, sodium alginate, calcium carbonate, sodium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and combinations thereof. In certain embodiments, the amount of disintegrant used in the pharmaceutical compositions provided herein is from about 0.5 to about 15 weight percent of disintegrant, while in other embodiments the amount is from about 1 to about 5 weight percent of disintegrant.

[000256] Non-limiting examples of such lubricants include, but are not limited to, sodium stearate, calcium stearate, magnesium stearate, stearic acid, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, sodium lauryl sulfate, talc, hydrogenated vegetable oil (by way of example only, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, sodium oleate, ethyl oleate, ethyl laureate, agar, silica, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, Md.), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, Tex.), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass.) and combinations thereof. In certain embodiments, the amount of lubricants used in the pharmaceutical compositions provided herein is in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms.

[000257] Non-limiting examples of such diluents include, but are not limited to, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycine or combinations thereof.

[000258] In certain embodiments, tablets and capsules are prepared by uniformly admixing at least one compound of Formula (I) (active ingredients) with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary. In certain embodiments, tablets are prepared by compression. In other embodiments, tablets are prepared by molding.

[000259] In certain embodiments, at least one compound of Formula (I) is orally administered as a controlled release dosage form. Such dosage forms are used to provide slow or controlled-release of one or more compounds of Formula (I). Controlled release is obtained using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof. In

certain embodiments, controlled-release dosage forms are used to extend activity of the compound of Formula (I), reduce dosage frequency, and increase patient compliance.

[000260] Administration of compounds of Formula (I) as oral fluids such as solution, syrups and elixirs are prepared in unit dosage forms such that a given quantity of solution, syrups or elixirs contains a predetermined amount of a compound of Formula (I). Syrups are prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions are formulated by dispersing the compound in a non-toxic vehicle. Non-limiting examples of excipients used in as oral fluids for oral administration include, but are not limited to, solubilizers, emulsifiers, flavoring agents, preservatives, and coloring agents. Non-limiting examples of solubilizers and emulsifiers include, but are not limited to, water, glycols, oils, alcohols, ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers. Non-limiting examples of preservatives include, but are not limited to, sodium benzoate. Non-limiting examples of flavoring agents include, but are not limited to, peppermint oil or natural sweeteners or saccharin or other artificial sweeteners.

Parenteral Dosage Forms

[000261] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) are administered parenterally by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial.

[000262] Such parenteral dosage forms are administered in the form of sterile or sterilizable injectable solutions, suspensions, dry and/or lyophylized products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection (reconstitutable powders) and emulsions. Vehicles used in such dosage forms include, but are not limited to, Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Transdermal Dosage Forms

[000263] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) are administered transdemally. Such transdermal dosage forms include "reservoir type" or "matrix type" patches, which are applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of a compound of Formula (I). By way of example

only, such transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. In other embodiments, matrix transdermal formulations are used.

[000264] Formulations for transdermal delivery of a compound of Formula (I) include an effective amount of a compound of Formula (I), a carrier and an optional diluent. A carrier includes, but is not limited to, absorbable pharmacologically acceptable solvents to assist passage through the skin of the host, such as water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and combinations thereof.

[000265] In certain embodiments, such transdermal delivery systems include penetration enhancers to assist in delivering one or more compounds of Formula (I) to the tissue. Such penetration enhancers include, but are not limited to, acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

[000266] In other embodiments, the pH of such a transdermal pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, is adjusted to improve delivery of one or more compounds of Formula (I). In other embodiments, the polarity of a solvent carrier, its ionic strength, or tonicity are adjusted to improve delivery. In other embodiments, compounds such as stearates are added to advantageously alter the hydrophilicity or lipophilicity of one or more compounds of Formula (I) so as to improve delivery. In certain embodiments, such stearates serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. In other embodiments, different salts, hydrates or solvates of the compounds of Formula (I) are used to further adjust the properties of the resulting composition.

Topical Dosage Forms

[000267] In certain embodiments at least one compound of Formula (I) is administered by topical application of pharmaceutical composition containing at least one compound of Formula (I) in the form of lotions, gels, ointments solutions, emulsions, suspensions or creams. Suitable formulations for topical application to the skin are aqueous solutions, ointments, creams or gels, while

formulations for ophthalmic administration are aqueous solutions. Such formulations optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[000268] Such topical formulations include at least one carrier, and optionally at least one diluent. Such carriers and diluents include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and combinations thereof.

[000269] In certain embodiments, such topical formulations include penetration enhancers to assist in delivering one or more compounds of Formula (I) to the tissue. Such penetration enhancers include, but are not limited to, acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

[000270] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) are administered by inhalation. Dosage forms for inhaled administration are formulated as aerosols or dry powders. Aerosol formulations for inhalation administration comprise a solution or fine suspension of at least one compound of Formula (I) in a pharmaceutically acceptable aqueous or non-aqueous solvent. In addition, such pharmaceutical compositions optionally comprise a powder base such as lactose, glucose, trehalose, mannitol or starch, and optionally a performance modifier such as L-leucine or another amino acid, and/or metals salts of stearic acid such as magnesium or calcium stearate.

[000271] In certain embodiments, compounds of Formula (I) are be administered directly to the lung by inhalation using a Metered Dose Inhaler ("MDI"), which utilizes canisters that contain a suitable low boiling propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or a Dry Powder Inhaler (DPI) device which uses a burst of gas to create a cloud of dry powder inside a container, which is then be inhaled by the patient. In certain embodiments, capsules and cartridges of gelatin for use in an inhaler or insufflator are formulated containing a powder mixture of a compound of Formula (I) and a powder base such as lactose or starch. In certain embodiments, compounds of Formula (I) are delivered to the lung using a liquid spray device, wherein such devices use extremely small nozzle holes to aerosolize liquid drug formulations that can then be directly inhaled into the lung. In other embodiments, compounds of Formula (I) are delivered to the lung using a nebulizer

device, wherein a nebulizers creates an aerosols of liquid drug formulations by using ultrasonic energy to form fine particles that can be readily inhaled. In other embodiments, compounds of Formula (I) are delivered to the lung using an electrohydrodynamic ("EHD") aerosol device wherein such EHD aerosol devices use electrical energy to aerosolize liquid drug solutions or suspensions.

[000272] In certain embodiments, the pharmaceutical composition containing at least one compound of Formula (I), or pharmaceutically acceptable salts and solvates thereof, described herein, also contain one or more absorption enhancers. In certain embodiments, such absorption enhancers include, but are not limited to, sodium glycocholate, sodium caprate, N-lauryl-β-D-maltopyranoside, EDTA, and mixed micelles.

[000273] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) are administered nasally. The dosage forms for nasal administration are formulated as aerosols, solutions, drops, gels or dry powders.

[000274] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) are administered rectally in the form of suppositories, enemas, ointment, creams rectal foams or rectal gels. In certain embodiments such suppositories are prepared from fatty emulsions or suspensions, cocoa butter or other glycerides.

[000275] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) are administered opthamically as eye drops. Such formulations are aqueous solutions that optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[000276] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) are administered otically as ear drops. Such formulations are aqueous solutions that optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[000277] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) are formulated as a depot preparation. Such long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. In certain embodiments, such formulations include polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[000278] Provided herein are compounds of Formula (I), pharmaceutically acceptable salts and solvates thereof, and pharmaceutical compositions containing at least one compound of Formula

(I) and/or pharmaceutically acceptable salts and solvates thereof, for use in modulating TLR activity, and thereby are used to in the prevention or treatment of diseases and/or disorders associated with TLR activity. In certain embodiments, such compounds of Formula (I), pharmaceutically acceptable salts and solvates thereof, and pharmaceutical compositions are agonists of TLR7, and thereby are used to in the treatment of diseases and/or disorders associated with TLR7. In certain embodiments, such compounds of Formula (I), pharmaceutically acceptable salts and solvates thereof, and pharmaceutical compositions are agonists of TLR8, and thereby are used to in the treatment of diseases and/or disorders associated with TLR8.

[000279] Also provided herein are methods for the treatment of a subject suffering from a disease and/or disorder associated with TLR activity, wherein the methods include administering to the subject an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, either alone or as part of a pharmaceutical composition as described herein.

[000280] Provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of a disease or disorder associated with TLR activity. In certain embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is used in the preparation of a medicament for the treatment of a disease or disorder associated with TLR7. In certain embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is used in the preparation of a medicament for the treatment of a disease or disorder associated with TLR8.

[000281] In a further embodiment, the pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for oral administration for the treatment of viral diseases and/or disorders associated with TLR7 or TLR8 activity.

[000282] In a further embodiment, the pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for oral administration for the treatment of infectious diseases and/or disorders associated with TLR7 or TLR8 activity.

[000283] In a further embodiment, the pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for oral administration for the treatment of bacterial diseases and/or disorders associated with TLR7 or TLR8 activity.

[000284] In a further embodiment, the pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for oral administration for the treatment of fungal diseases and/or disorders associated with TLR7 or TLR8 activity.

[000285] In a further embodiment, the pharmaceutical compositions comprising at least one

compound of Formula (I) are adapted for oral administration for the treatment of cancer associated with TLR7 or TLR8 activity.

[000286] In a further embodiment, the pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for intravenous administration for the treatment of cancer associated with TLR7 or TLR8 activity.

[000287] In a further embodiment, the pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for oral administration for the treatment of allograft rejection diseases and/or disorders associated with TLR7 or TLR8 activity.

[000288] In a further embodiment, the pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for oral administration for the treatment of genitourinary diseases and/or disorders associated with TLR7 or TLR8 activity.

[000289] In a further embodiment, the pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for administration as eye drops for the treatment of ophthalmic diseases and/or disorders associated with TLR7 or TLR8 activity.

[000290] In a further embodiment, the pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for topical administration for the treatment of dermatological diseases and/or disorders associated with TLR7 or TLR8 activity.

[000291] In a further embodiment, the pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for topical administration for the treatment of actinic keratosis. In a further embodiment, the pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for topical administration as a cream for the treatment of actinic keratosis.

[000292] In a further embodiment, the pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for topical administration for the treatment of basal cell carcinoma. In a further embodiment, the pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for topical administration as a cream for the treatment of basal cell carcinoma.

[000293] In a further embodiment, the pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for administration by inhalation for the treatment of respiratory diseases and/or disorders associated with TLR7 or TLR8 activity. In certain embodiments, the respiratory disease is allergic asthma.

Combination Treatment

[000294] In certain embodiments, a compound of Formulas (I)-(XVI) described herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I)-(XVI) described herein, is administered alone (without an additional therapeutic agent) for the treatment of one or more of the disease and/or disorders associated with TLR activity described herein.

[000295] In other embodiments, a compound of Formulas (I)-(XVI) described herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I)-(XVI) described herein, is administered in combination with one or more additional therapeutic agents, for the treatment of one or more of the disease and/or disorders associated with TLR activity described herein.

[000296] In other embodiments, a compound of Formulas (I)-(XVI) described herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I)-(XVI) described herein, is formulated in combination with one or more additional therapeutic agents and administered for the treatment of one or more of the disease and/or disorders associated with TLR activity described herein.

[000297] In a compound of Formulas (I)-(XVI) described herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I)-(XVI) described herein, is administered sequentially with one or more additional therapeutic agents, for the treatment of one or more of the disease and/or disorders associated with TLR activity described herein.

[000298] In other embodiments, the combination treatments provided herein include administration of a compound of Formula (I)-(XVI) described herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing a compound of Formula (I)-(XVI), prior to administration of one or more additional therapeutic agents, for the treatment of one or more of the disease and/or disorders associated with TLR activity described herein.

[000299] In other embodiments, the combination treatments provided herein include administration of a compound of Formula (I)-(XVI) described herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing a compound of Formula (I)-(XVI), subsequent to administration of one or more additional therapeutic agents, for the treatment of one or more of the disease and/or disorders associated with TLR activity described herein.

[000300] In certain embodiments, the combination treatments provided herein include administration of a compound of Formula (I)-(XVI) described herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing a compound of Formula (I)-(XVI), concurrently with one or more additional therapeutic agents, for the treatment of one or more of the disease and/or disorders associated with TLR activity described herein.

[000301] In certain embodiments, the combination treatments provided herein include administration of a compound of Formula (I)-(XVI) described herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing a compound of Formula (I)-(XVI) formulated with one or more additional therapeutic agents, for the treatment of one or more of the disease and/or disorders associated with TLR activity described herein.

[000302] In certain embodiments of the combination treatments described herein the compounds of Formula (I), or a pharmaceutically acceptable salts or solvates thereof, are modulators of TLR activity. In certain embodiments of the combination treatments described herein the compounds of Formula (I), or a pharmaceutically acceptable salts or solvates thereof, are TLR7 agonists. In certain embodiments of the combination treatments described herein the compounds of Formula (I), or a pharmaceutically acceptable salts or solvates thereof, are TLR8 agonists.

[000303] In certain embodiments of the combination therapies described herein, the compounds of Formula (I) described herein, or a pharmaceutically acceptable salts or solvates thereof, and the additional therapeutics agent(s) act additively. In certain embodiments of the combination therapies described herein, the compounds of Formula (I) described herein, or a pharmaceutically acceptable salts or solvates thereof, and the additional therapeutics agent(s) act synergistically.

[000304] In other embodiments, a compound of Formula (I) described herein, or a pharmaceutically acceptable salts or solvates thereof, or a pharmaceutical composition containing a compound of Formula (I), is administered to a patient who has not previously undergone or is not currently undergoing treatment with another therapeutic agent.

[000305] The additional therapeutic agents used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to antibiotics or antibacterial agents, antiemetic agents, antifungal agents, anti-inflammatory agents, antiviral agents, immunomodulatory agents, cytokines, antidepressants, hormones, alkylating agents, antimetabolites, antitumour antibiotics, antimitotic agents, topoisomerase inhibitors, cytostatic agents, anti-invasion agents, antiangiogenic agents, inhibitors of growth factor function inhibitors of viral replication, viral enzyme inhibitors, anticancer agents,

α-interferons, β-interferons, ribavirin, hormones, cytokines, and other toll-like receptor modulators.

[000306] The antibiotics or antibacterial agents used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, valganciclovir hydrochloride, metronidazole, a beta-lactam, macrolides (such as, by way of example only, azithromycin, tobramycin (TOBI™)), cephalosporins (such as, by way of example only, cefaclor, cefadroxil, cephalexin, cephradine, cefamandole, cefatrizine, cefazedone, cefixime, cefozopran, cefpimizole, cefuroxime, cefpiramide, cefprozil, cefpirome, KEFLEX™, VELOSEF™, CEFTIN™, CEFZIL™, CECLOR™, SUPRAX™ and DURICEF™), a clarithromycin (such as, by way of example only, clarithromycin and BIAXIN™), an erythromycin (such as, by way of example only, erythromycin and EMYCIN™), ciprofloxacin, CIPRO™, a norfloxacin (such as, by way of example only, NOROXIN™), aminoglycoside antibiotics (such as, by way of example only, apramycin, arbekacin, bambermycins, butirosin, dibekacin, neomycin, neomycin, undecylenate, netilmicin, paromomycin, ribostamycin, sisomicin, and spectinomycin), amphenicol antibiotics (such as, by way of example only, azidamfenicol, chloramphenicol, florfenicol, and thiamphenicol), ansamycin antibiotics (such as, by way of example only, rifamide and rifampin), carbacephems (such as, by way of example only, loracarbef), carbapenems (such as, by way of example only, biapenem and imipenem), cephamycins (such as, by way of example only, cefbuperazone, cefmetazole, and cefminox), monobactams (such as, by way of example only, aztreonam, carumonam, and tigemonam), oxacephems (such as, by way of example only, flomoxef, and moxalactam), penicillins (such as, by way of example only, amdinocillin, amdinocillin pivoxil, amoxicillin, bacampicillin, benzylpenicillinic acid, benzylpenicillin sodium, epicillin, fenbenicillin, floxacillin, penamccillin, penethamate hydriodide, penicillin o-benethamine, penicillin 0, penicillin V, penicillin V benzathine, penicillin V hydrabamine, penimepicycline, phencihicillin potassium, V-CILLIN K™ and PEN VEE K™), lincosamides (such as, by way of example only, clindamycin, and lincomycin), amphomycin, bacitracin, capreomycin, colistin, enduracidin, enviomycin, tetracyclines (such as, by way of example only, apicycline, chlortetracycline, clomocycline, and demeclocycline), 2,4-diaminopyrimidines (such as, by way of example only, brodimoprim), nitrofurans (such as, by way of example only, furaltadone, and furazolium chloride), quinolones and analogs thereof (such as, by way of example only, a fluoroquinolone, ofloxacin, cinoxacin, clinafloxacin, flumequine, grepagloxacin and FLOXIN™), sulfonamides (such as, by way of

example only, acetyl sulfamethoxypyrazine, benzylsulfamide, noprylsulfamide, phthalylsulfacetamide, sulfachrysoidine, and sulfacytine), sulfones (such as, by way of example only, diathymosulfone, glucosulfone sodium, and solasulfone), cycloserine, mupirocin, tuberin and combinations thereof.

[000307] The antiemetic agents used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, metoclopromide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acethylleucine monoethanolamine, alizapride, azasetron, benzquinamide, bietanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxyperndyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinols, thiethylperazine, thioproperazine, tropisetron, and combinations thereof.

[000308] The antifungal agents used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, amphotericin B, itraconazole, ketoconazole, fluconazole, fosfluconazole, intrathecal, flucytosine, miconazole, butoconazole, itraconazole, clotrimazole, nystatin, terconazole, tioconazole, voriconazole, ciclopirox, econazole, haloprogrin, naftifine, terbinafine, undecylenate, and griseofulvin.

[000309] The anti-inflammatory agents used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, non-steroidal anti-inflammatory drugs such as salicylic acid, acetylsalicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, acetaminophen, indomethacin, sulindac, etodolac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, dichlofenac, ibuprofen, naproxen, naproxen sodium, fenoprofen, ketoprofen, flurbinprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, droxicam, pivoxicam, tenoxicam, nabumetome, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone and nimesulide, leukotriene antagonists including, but not limited to, zileuton, aurothioglucose, gold sodium thiomalate and auranofin, steroids including, but not limited to, alclometasone diproprionate, amcinonide, beclomethasone dipropionate, betametasone, betamethasone benzoate, betamethasone diproprionate, betamethasone sodium phosphate, betamethasone valerate, clobetasol proprionate, clocortolone pivalate, hydrocortisone, hydrocortisone derivatives, desonide, desoximatasone, dexamethasone, flunisolide, flucoxinolide, flurandrenolide, halcinocide, medrysone,

methylprednisolone, methprednisolone acetate, methylprednisolone sodium succinate, mometasone furoate, paramethasone acetate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebuatate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate, and triamcinolone hexacetonide and other anti-inflammatory agents including, but not limited to, methotrexate, colchicine, allopurinol, probenecid, thalidomide or a derivative thereof, 5-aminosalicylic acid, retinoid, dithranol or calcipotriol, sulfinpyrazone and benzbromarone.

[000310] The antiviral agents used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, protease inhibitors, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), CCR1 antagonist, CCR5 antagonists, and nucleoside analogs. The antiviral agents include but are not limited to fomivirsen, didanosine, lamivudine, stavudine, zalcitabine, zidovudine, acyclovir, famciclovir, valaciclovir, ganciclovir, gangcyclovir, cidofovir, zanamivir, oseltamavir, vidarabine, idoxuridine, trifluridine, levovirin, viramidine and ribavirin, as well as foscarnet, amantadine, rimantadine, saquinavir, indinavir, nelfinavir, amprenavir, lopinavir, ritonavir, the α-interferons; β-interferons; adefovir, clevadine, entecavir, pleconaril, HCV-086, EMZ702, emtricitabine, celgosivir, valopicitabine, inhibitors of HCV protease, such as BILN 2061, SCH-503034, ITMN-191 or VX-950, inhibitors of NS5B polymerase such as NM107 (and its prodrug NM283), R1626, R7078, BILN1941, GSK625433, GILD9128 or HCV-796, efavirenz, HBY-097, nevirapine, TMC-120 (dapivirine), TMC-125, BX-471, etravirine, delavirdine, DPC-083, DPC-961, capravirine, rilpivirine, 5-{[3,5-diethyl-1-(2-hydroxyethyl)-1H-pyrazol-4-yl]oxy}isophthalonitrile, GW-678248, GW-695634, MIV-150, calanolide, TAK-779, SC-351125, ancriviroc, vicriviroc, maraviroc, PRO-140, aplaviroc 40, Ono-4128, AK-602), AMD-887 CMPD-167, methyl 1-endo-{8-[(3S)-3-(acetylamino)-3-(3-fluorophenyl)propyl]-8-azabicyclo[3.- 2.1]oct-3-yl}-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-5-carboxylate, methyl 3-endo-{8-[(3S)-3-(acetamido)-3-(3-fluorophenyl)propyl]-8-azabicyclo[3.2.- 1]oct-3-yl}-2-methyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine-5-carboxylate, ethyl 1-endo-{8-[(3S)-3-(acetylamino)-3-(3-fluorophenyl)propyl]-8-azabicyclo[3.-2.1]oct-3-yl}-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-5-carboxylate, and N-{(1S)-3-[3-endo-(5-Isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,- 5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propyl}acetamide), BMS-806, BMS-488043, 5-{(1S)-2-[(2R)-4-benzoyl-2-methyl-piperazin-1-yl]-1-methyl-2-oxo-ethoxy}-4-methoxy-pyridine-

2-carboxylic acid methylamide and 4-{(1S)-2-[(2R)-4-benzoyl-2-methyl-piperazin-1-yl]-1-methyl-2-oxo-ethoxy}-3-methoxy-N-methyl-benzamide, enfuvirtide (T-20), sifuvirtide SP-01A, T1249, PRO 542, AMD-3100, soluble CD4, HMG CoA reductase inhibitors, atorvastatin, 3-O-(3'3'-dimethylsuccinyl) betulic acid (otherwise known as PA-457) and αHGA.

[000311] The immunomodulatory agents used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, azathioprine, tacrolimus, cyclosporin methothrexate, leflunomide, corticosteroids, cyclophosphamide, cyclosporine A, cyclosporin G, mycophenolate mofetil, ascomycin, rapamycin (sirolimus), FK-506, mizoribine, deoxyspergualin, brequinar, mycophenolic acid, malononitriloamindes (such as, by way of example only, leflunamide), T cell receptor modulators, and cytokine receptor modulators, peptide mimetics, and antibodies (such as, by way of example only, human, humanized, chimeric, monoclonal, polyclonal, Fvs, ScFvs, Fab or F(ab)2 fragments or epitope binding fragments), nucleic acid molecules (such as, by way of example only, antisense nucleic acid molecules and triple helices), small molecules, organic compounds, and inorganic compounds. Examples of T cell receptor modulators include, but are not limited to, anti-T cell receptor antibodies (such as, by way of example only, anti-CD4 antibodies (such as, by way of example only, cM-T412 (Boehringer), IDEC-CE9.1™ (IDEC and SKB), mAB 4162W94, Orthoclone and OKTcdr4a (Janssen-Cilag)), anti-CD3 antibodies (such as, by way of example only, Nuvion (Product Design Labs), OKT3 (Johnson & Johnson), or Rituxan (IDEC)), anti-CD5 antibodies (such as, by way of example only, an anti-CD5 ricin-linked immunoconjugate), anti-CD7 antibodies (such as, by way of example only, CHH-380 (Novartis)), anti-CD8 antibodies, anti-CD40 ligand monoclonal antibodies (such as, by way of example only, IDEC-131 (IDEC)), anti-CD52 antibodies (such as, by way of example only, CAMPATH 1H (Ilex)), anti-CD2 antibodies, anti-CD11a antibodies (such as, by way of example only, Xanelim (Genentech)), anti-B7 antibodies (such as, by way of example only, IDEC-114 (IDEC)), CTLA4-immunoglobulin, and other toll receptor-like (TLR) modulators. Examples of cytokine receptor modulators include, but are not limited to, soluble cytokine receptors (such as, by way of example only, the extracellular domain of a TNF-α receptor or a fragment thereof, the extracellular domain of an IL-1β receptor or a fragment thereof, and the extracellular domain of an IL-6 receptor or a fragment thereof), cytokines or fragments thereof (such as, by way of example only, interleukin (IL)-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-15, TNF-.alpha., interferon (IFN)-α, IFN-β, IFN-γ, and GM-CSF), anti-cytokine receptor antibodies (such as, by way of example only,

anti-IFN receptor antibodies, anti-IL-2 receptor antibodies (such as, by way of example only, Zenapax (Protein Design Labs)), anti-IL-4 receptor antibodies, anti-IL-6 receptor antibodies, anti-IL-10 receptor antibodies, and anti-IL-12 receptor antibodies), anti-cytokine antibodies (such as, by way of example only, anti-IFN antibodies, anti-TNF-α antibodies, anti-IL-1β antibodies, anti-IL-6 antibodies, anti-IL-8 antibodies (such as, by way of example only, ABX-IL-8 (Abgenix)), and anti-IL-12 antibodies).

[000312] The cytokines or modulator of cytokine function used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-9 (IL-9), interleukin-10 (IL-10), interleukin-12 (IL-12), interleukin 15 (IL-15), interleukin 18 (IL-18), platelet derived growth factor (PDGF), erythropoietin (Epo), epidermal growth factor (EGF), fibroblast growth factor (FGF), granulocyte macrophage stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), macrophage colony stimulating factor (M-CSF), prolactin, alpha-, beta-, and gamma-interferon, interferon β-1a, interferon β-1b, interferon α-1, interferon α-2a (roferon), interferon α-2b, pegylated interferons (by way of example only, peginterferon α-2a and peginterferon α-2b), intron, Peg-Intron, Pegasys, consensus interferon (infergen), albumin-interferon α and albuferon.

[000313] The antidepressants used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, binedaline, caroxazone, citalopram, dimethazan, fencamine, indalpine, indeloxazine hydrocholoride, nefopam, nomifensine, oxitriptan, oxypertine, paroxetine, sertraline, thiazesim, trazodone, benmoxine, echinopsidine iodide, etryptamine, iproclozide, iproniazid, isocarboxazid, mebanazine, metfendrazine, nialamide, pargyline, octamoxin, phenelzine, pheniprazine, phenoxypropazine, pivhydrazine, safrazine, selegiline, l-deprenyl, cotinine, rolicyprine, rolipram, maprotiline, metralindole, mianserin, mirtazepine, adinazolam, amitriptyline, amitriptylinoxide, amoxapine, butriptyline, clomipramine, demexiptiline, desipramine, dibenzepin, dimetacrine, dothiepin, doxepin, fluacizine, imipramine, imipramine N-oxide, iprindole, lofepramine, melitracen, metapramine, nortriptyline, noxiptilin, opipramol, pizotyline, propizepine, protriptyline, quinupramine, tianeptine, trimipramine, adrafinil, benactyzine, bupropion, butacetin, dioxadrol, duloxetine, etoperidone, febarbamate, femoxetine, fenpentadiol, fluoxetine, fluvoxamine, hematoporphyrin, hypericin, levophacetoperane, medifoxamine, milnacipran,

minaprine, moclobemide, nefazodone, oxaflozane, piberaline, prolintane, pyrisuccideanol, ritanserin, roxindole, rubidium chloride, sulpiride, tandospirone, thozalinone, tofenacin, toloxatone, tranylcypromine, L-tryptophan, venlafaxine, viloxazine, and zimeldine.

[000314] In certain embodiments, the antidepressants used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, are MAO-inhibitors including, but are not limited to, benmoxin, echinopsidine iodide, etryptamine, iproclozide, iproniazid, isocarboxazid, mebanazine, metfendrazine, moclobamide, nialamide, pargyline, phenelzine, pheniprazine, phenoxypropazine, pivhydrazine, safrazine, selegiline, l-deprenyl, toloxatone and tranylcypromine.

[000315] The hormones used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, luteinizing hormone releasing hormone (LHRH), growth hormone (GH), growth hormone releasing hormone, ACTH, somatostatin, somatotropin, somatomedin, parathyroid hormone, hypothalamic releasing factors, insulin, glucagon, enkephalins, vasopressin, calcitonin, heparin, low molecular weight heparins, heparinoids, thymostimulin, synthetic and natural opioids, insulin thyroid stimulating hormones, and endorphins.

[000316] The alkylating agents used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, nitrogen mustards, ethylenimines, methylmelamines, alkyl sulfonates, nitrosoureas, carmustine, lomustine, triazenes, melphalan, mechlorethamine, cis-platin, oxaliplatin, carboplatin, cyclophosphamide, ifosfamide, melphalan, chlorambucil, hexamethylmelaine, thiotepa, busulfan, carmustine, streptozocin, dacarbazine and temozolomide.

[000317] The antimetabolites used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, cytarabile, gemcitabine and antifolates such as, by way of example only, fluoropyrimidines (by way of example only, 5-fluorouracil and tegafur), raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea.

[000318] The antitumour antibiotics in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, anthracyclines, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin.

[000319] The antimitotic agents used in combination with at least one compound of Formula (I)

described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, vinca alkaloids (by way of example only, vincristine, vinblastine, vindesine and vinorelbine), taxoids (by way of example only, taxol, paclitaxel and taxotere) and polokinase inhibitors.

[000320] The topoisomerase inhibitors used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, epipodophyllotoxins by way of example only, etoposide and teniposide, amsacrine, topotecan, irinotecan and camptothecin.

[000321] The cytostatic agents used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, antioestrogens (such as, by way of example only, tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (such as, by way of example only, bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (such as, by way of example only, goserelin, leuprorelin, leuprolide and buserelin), progestogens (such as, by way of example only, megestrol acetate), aromatase inhibitors (such as, by way of example only, as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase (such as, by way of example only, finasteride).

[000322] The anti-invasion agents used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, c-Src kinase family inhibitors (such as, by way of example only, 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530) and N-(2- chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4- ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825)), and metalloproteinase inhibitors (such as, by way of example only, marimastat, inhibitors of urokinase plasminogen activator receptor function andantibodies to Heparanase).

[000323] The antiangiogenic agents used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, those which inhibit the effects of vascular endothelial growth factor such as, by way of example only, anti-vascular endothelial cell growth factor antibody bevacizumab (AVASTIN™) and VEGF receptor tyrosine kinase inhibitors such as 4-(4-bromo- 2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3- pyrrolidin- 1 -ylpropoxy)quinazoline (AZD2171), vatalanib (PTK787) and SU1

1248 (sunitinib), linomide, and inhibitors of integrin αvβ3 function and angiostatin.

[000324] The inhibitors of growth factor function used in combination with at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to, growth factor antibodies and growth factor receptor antibodies (such as, by way of example only, the anti-erbB2 antibody trastuzumab (HERCEPTIN™), the anti-EGFR antibody panitumumab, the anti-erbBl antibody cetuximab (Erbitux, C225), tyrosine kinase inhibitors, such as, by way of example only, inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as, by way of example only, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-orpholinopropoxy)quinazolin-4-amine (gefitinib, ZDl 839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3- morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as, by way of example only, lapatinib, inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth factor family such as imatinib, GLEEVEC™, inhibitors of serine/threonine kinases (such as, by way of example only, Ras/Raf signaling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)), inhibitors of cell signalling through MEK and/or AKT kinases, inhibitors of the hepatocyte growth factor family, c-kit inhibitors, abl kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZDl 152, PH739358, VX-680, MLv8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors.

[000325] In other embodiments, at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, is used in combination with vascular damaging agents such as, by way of example only, Combretastatin A4.

[000326] In other embodiments, at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, is used in combination with antisense therapies, such as, by way of example only, ISIS 2503, an anti-ras antisense.

[000327] In other embodiments, at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, is used in combination with gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCAl or BRCA2, GDEPT (gene-directed enzyme pro-drug s therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug

resistance gene therapy.

[000328] In other embodiments, at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, is used in combination with immunotherapy approaches, including for example *ex-vivo* and *in-vivo* approaches to increase the immunogenicity of patient tumor cells, such as transfection with cytokines such o as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumor cell lines and approaches using anti-idiotypic antibodies.

[000329] In other embodiments, at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, is used in combination with other treatment methods including, but not limited to, surgery and radiotherapy (γ-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes).

[000330] In certain embodiments, the compounds of Formula (I) described herein, or pharmaceutically acceptable salts and solvates thereof, are administered or formulated in combination with an absorption enhancer, including, but not limited to, sodium glycocholate, sodium caprate, N-lauryl-β-D-maltopyranoside, EDTA, and mixed micelles. In certain embodiments, such absorption enhancers target the lymphatic system.

[000331] In certain embodiments, the additional therapeutic agent(s) used in the combination therapies described herein include, but are not limited to, agents such as tumor necrosis factor alpha (TNF-α) inhibitors (such as anti-TNF monoclonal antibodies (by way of example only, Remicade, CDP-870 and adalimumab) and TNF receptor immunoglobulin molecules (by way of example only, Enbrel)); non-selective cyclo-oxygenase COX-l/COX-2 inhibitors (by way of example only, piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin), COX-2 inhibitors (by way of example only, meloxicam, celecoxib, rofecoxib, valdecoxib, lumarocoxib, parecoxib and etoricoxib); glucocorticosteroids; methotrexate, lefunomide; hydroxychloroquine, d-penicillamine, auranofin or other parenteral or oral gold preparations.

[000332] In other embodiments, the combinations described herein include combination of a compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, with a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-

lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert- butylphenolhydrazones; a methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2- cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as MK-591, MK-886, and BAYx1005.

[000333] In other embodiments, the combinations described herein include combination of a compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, with a receptor antagonist for leukotrienes (LT B4, LTC4, LTD4, and LTE4) selected from the group consisting of the phenothiazin-3-ls such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, SINGULAIR™, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAYx7195.

[000334] In other embodiments, the combinations described herein include combination of a compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, with a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor, including, but not limited to, cilomilast or roflumilast, an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

[000335] In other embodiments, the combinations described herein include combination of a compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, with a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine.

[000336] In other embodiments, the combinations described herein include combination of a compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, with a gastroprotective histamine type 2 receptor antagonist. In other embodiments, the combinations described herein include combination of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, described herein, with an antagonist of the histamine type 4 receptor.

[000337] In other embodiments, the combinations described herein include combination of a compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate

thereof, with an alpha-l/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

[000338] In other embodiments, the combinations described herein include combination of a compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, with an anticholinergic agent including muscarinic receptor (Ml, M2, and M3) antagonists such as atropine, hyoscine, glycopyrrrolate, ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine or telenzepine.

[000339] In other embodiments, the combinations described herein include combination of a compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, with a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, albuterol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, and pirbuterol.

[000340] In other embodiments, the combinations described herein include combination of a compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, with a chromone, such as sodium cromoglycate or nedocromil sodium.

[000341] In other embodiments, the combinations described herein include combination of a compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, with an insulin-like growth factor type I (IGF-I) mimetic.

[000342] In other embodiments, the combinations described herein include combination of a compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, with a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

[000343] In other embodiments, the combinations described herein include combination of a compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, with an inhibitor of matrix metalloproteases (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-I), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-IO), and stromelysin-3 (MMP-Il) andMMP-9 and MMP-12.

[000344] In other embodiments, the combinations described herein include combination of a compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate

thereof, with modulators of chemokine receptor function such as antagonists of CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR1 1 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX3CR1 for the C-X3-C family.

[000345] In other embodiments, the combinations described herein include combination of a compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, with an immunoglobulin (Ig), gamma globulin, Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (omalizumab).

Compounds of Formula (I) as Immune Potentiators

[000346] In certain embodiments, pharmaceutical compositions containing at least one compound of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, are immunogenic compositions. In certain embodiments, such immunogenic compositions are useful as vaccines. In certain embodiments, such vaccines are prophylactic (*i.e.* to prevent infection), while in other embodiments, such vaccines are therapeutic (*i.e.* to treat infection).

[000347] In other embodiments, the compound(s) of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, are immune potentiators and impart an immunostimulatory effect upon administration when compared to immunogenic formulations that do not contain compound(s) of Formula (I). In certain embodiments, compounds of Formula (I) impart an immunostimulatory effect upon administration when included in an immunogenic composition having one or more immunoregulatory agents, while in other embodiments, compounds of Formula (I) impart an immunostimulatory effect upon administration when included in an immunogenic composition without the presence of other immunoregulatory agents.

[000348] The immunostimulatory effect referred to herein is often an enhancement of the immunogenic composition's effect. In certain embodiments the enhancement of the efficacy of the immunogenic composition is by at least 10% relative to the effect of the immunogenic composition in the absence of the immune potentiator. In certain embodiments the enhancement of the efficacy of the immunogenic composition is by at least 20% relative to the effect of the immunogenic composition in the absence of the immune potentiator. In certain embodiments the enhancement of the efficacy of the immunogenic composition is by at least 30% relative to the effect of the immunogenic composition in the absence of the immune potentiator. In certain embodiments the enhancement of the efficacy of the immunogenic composition is by at least 40%

relative to the effect of the immunogenic composition in the absence of the immune potentiator. In certain embodiments the enhancement of the efficacy of the immunogenic composition is by at least 50% relative to the effect of the immunogenic composition in the absence of the immune potentiator. In certain embodiments the enhancement of the efficacy of the immunogenic composition is by at least 60% relative to the effect of the immunogenic composition in the absence of the immune potentiator. In certain embodiments the enhancement of the efficacy of the immunogenic composition is by at least 70% relative to the effect of the immunogenic composition in the absence of the immune potentiator. In certain embodiments the enhancement of the efficacy of the immunogenic composition is by at least 80% relative to the effect of the immunogenic composition in the absence of the immune potentiator. In certain embodiments the enhancement of the efficacy of the immunogenic composition is by at least 90% relative to the effect of the immunogenic composition in the absence of the immune potentiator. In certain embodiments the enhancement of the efficacy of the immunogenic composition is by at least 100% relative to the effect of the immunogenic composition in the absence of the immune potentiator.

[000349] In certain embodiments, the enhancement of the immunogenic composition's effect is measured by the increased effectiveness of the immunogenic composition for achieving its protective effects. In certain embodiments, this increased effectiveness is measured as a decreased probability that a subject receiving the immunogenic composition will experience a condition for which the immunogenic composition is considered protective, or a decrease in duration or severity of the effects of such condition. In other embodiments, this increased effectiveness is measured as an increase in a titer of an antibody elicited by the immunogenic composition in a treated subject.

[000350] Along with one or more compounds of Formula (I) described herein, or a pharmaceutically acceptable salt or solvate thereof, such immunogenic compositions include an effective amount of one or more antigens, and a pharmaceutically acceptable carrier. Such carriers are include, but are not limited to, proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, sucrose, trehalose, lactose, lipid aggregates (such as oil droplets or liposomes), and inactive virus particles. The immunogenic compositions typically also contain diluents, such as water, saline, and glycerol, and optionally contain other excipients, such as wetting or emulsifying agents, and pH buffering substances.

[000351] In certain embodiments, immunogenic compositions optionally include one or more immunoregulatory agents. In certain embodiments, one or more of the immunoregulatory agents

include one or more adjuvants. Such adjuvants include, but are not limited to, a TH1 adjuvant and/or a TH2 adjuvant, further discussed below. In certain embodiments, the adjuvants used in immunogenic compositions provide herein include, but are not limited to:

A. Mineral-Containing Compositions;
B. Oil Emulsions;
C. Saponin Formulations;
D. Virosomes and Virus-Like Particles;
E. Bacterial or Microbial Derivatives;
F. Human Immunomodulators;
G. Bioadhesives and Mucoadhesives;
H. Microparticles;
I. Liposomes;
J. Polyoxyethylene Ether and Polyoxyethylene Ester Formulations;
K. Polyphosphazene (PCPP);
L. Muramyl Peptides, and
M. Imidazoquinolone Compounds.

[000352] Mineral-containing compositions suitable for use as adjuvants include, but are not limited to, mineral salts, such as aluminium salts and calcium salts. By way of example only, such mineral salts include, hydroxides (e.g. oxyhydroxides, including aluminium hydroxides and aluminium oxyhydroxides), phosphates (e.g. hydroxyphosphates and orthophosphates, including aluminium phosphates, aluminium hydroxyphosphates, aluminium orthophosphates and calcium phosphate), sulfates (e.g. aluminium sulfate), or mixtures of different mineral compounds. Such mineral salts are in any suitable form, such as, by way of example only, gel, crystalline, and amorphous forms. In certain embodiments, such mineral containing compositions are formulated as a particle of the metal salt. In certain embodiments, components of the immunogenic compositions described herein are adsorbed to such mineral salts. In certain embodiments, an aluminium hydroxide and/or aluminium phosphate adjuvant is used in the immunogenic compositions described herein. In other embodiments, antigens used in an immunogenic composition described herein are adsorbed to such aluminium hydroxide and/or aluminium phosphate adjuvants. In certain embodiments, a calcium phosphate adjuvant is used in the immunogenic compositions described herein. In other embodiments, antigens used in an immunogenic composition described herein are adsorbed to such calcium phosphate adjuvants.

[000353] In certain embodiments, aluminum phosphates are used as an adjuvant in the immunogenic compositions described herein. In other embodiments, aluminum phosphates are used as an adjuvant in the immunogenic compositions described herein, wherein such compositions include a *H.influenzae* saccharide antigen. In certain embodiments, the adjuvant is amorphous aluminium hydroxyphosphate with a PO_4/Al molar ratio between 0.84 and 0.92,

included at 0.6mg Al^{3+}/ml. In other embodiments, adsorption with a low dose of aluminium phosphate is used, by way of example only, between 50 and 100μg Al^{3+} per conjugate per dose. Where there is more than one conjugate in a composition, not all conjugates need to be adsorbed.

[000354] Oil emulsions suitable for use as adjuvants include, but are not limited to, squalene-water emulsions (such as MF59 (5% Squalene, 0.5% Tween 80, and 0.5% Span 85, formulated into submicron particles using a microfluidizer), Complete Freund's adjuvant (CFA) and incomplete Freund's adjuvant (IFA).

[000355] Saponins are a heterologous group of sterol glycosides and triterpenoid glycosides that are found in the bark, leaves, stems, roots and even flowers of a wide range of plant species. Saponin formulations suitable for use as adjuvants include, but are not limited to, saponins from the bark of the Quillaia saponaria Molina tree, from Smilax ornata (sarsaprilla), Gypsophilla paniculata (brides veil), and Saponaria officianalis (soap root). In certain embodiments, saponin formulations suitable for use as adjuvants include, but are not limited to, purified formulations including, but are not limited to, QS7, QS17, QS18, QS21, QH-A, QH-B and QH-C. QS21 is marketed as STIMULOM™. In other embodiments, saponin formulations include sterols, cholesterols and lipid formulations, such as unique particles formed by the combinations of saponins and cholesterols called immunostimulating complexes (ISCOMs). In certain embodiments, the ISCOMs also include a phospholipid such as phosphatidylethanolamine or phosphatidylcholine. Any known saponin can be used in ISCOMs. In certain embodiments, the ISCOM includes one or more of QuilA, QHA & QHC. In other embodiments, the ISCOMS are optionally devoid of an additional detergent.

[000356] Virosomes and virus-like particles (VLPs) suitable for use as adjuvants include, but are not limited to, one or more proteins from a virus optionally combined or formulated with a phospholipid. Such virosomes and VLPs are generally non-pathogenic, non-replicating and generally do not contain any of the native viral genome. In certain embodiments, the viral proteins are recombinantly produced, while in other embodiments the viral proteins are isolated from whole viruses.

[000357] The viral proteins suitable for use in virosomes or VLPs include, but are not limited to, proteins derived from influenza virus (such as HA or NA), Hepatitis B virus (such as core or capsid proteins), Hepatitis E virus, measles virus, Sindbis virus, Rotavirus, Foot-and-Mouth Disease virus, Retrovirus, Norwalk virus, human Papilloma virus, HIV, RNA-phages, Qβ-phage (such as coat proteins), GA-phage, fr-phage, AP205 phage, and Ty (such as retrotransposon Ty

protein p1).

[000358] Bacterial or microbial derivatives suitable for use as adjuvants include, but are not limited to, bacterial or microbial derivatives such as non-toxic derivatives of enterobacterial lipopolysaccharide (LPS), Lipid A derivatives, immunostimulatory oligonucleotides and ADP-ribosylating toxins and detoxified derivatives thereof. Such non-toxic derivatives of LPS include, but are not limited to, monophosphoryl lipid A (MPL) and 3-O-deacylated MPL (3dMPL). 3dMPL is a mixture of 3 de-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated chains. Other non-toxic LPS derivatives include monophosphoryl lipid A mimics, such as aminoalkyl glucosaminide phosphate derivatives (e.g. RC-529). Lipid A derivatives include, but are not limited to, derivatives of lipid A from Escherichia coli (e.g. OM-174).

[000359] Immunostimulatory oligonucleotides used as adjuvants include, but are not limited to, nucleotide sequences containing a CpG motif (a dinucleotide sequence containing an unmethylated cytosine linked by a phosphate bond to a guanosine). Such CpG sequences can be double-stranded or single-stranded. In certain embodiments, such nucleotide sequences are double-stranded RNAs or oligonucleotides containing palindromic or poly(dG) sequences. In other embodiments, the CpG's include nucleotide modifications/analogs such as phosphorothioate modifications.

[000360] In certain embodiments the CpG sequence are directed to TLR9, and in certain embodiments the motif is GTCGTT or TTCGTT. In certain embodiments the CpG sequence is specific for inducing a Th1 immune response, such as, by way of example only, a CpG-A ODN, or in other embodiments the CpG sequence is more specific for inducing a B cell response, such as, by way of example only, a CpG-B ODN. In certain embodiments the CpG is a CpG-A ODN.

[000361] In certain embodiments the CpG oligonucleotide is constructed so that the 5' end is accessible for receptor recognition. In other embodiments two CpG oligonucleotide sequences are optionally attached at their 3' ends to form "immunomers".

[000362] A particularly useful adjuvant based around immunostimulatory oligonucleotides is known as IC-31™. In certain embodiments, an adjuvant used with immunogenic compositions described herein, includes a mixture of (i) an oligonucleotide (such as, by way of example only, between 15-40 nucleotides) including at least one (and preferably multiple) CpI motifs (such as, by way of example only, a cytosine linked to an inosine to form a dinucleotide), and (ii) a polycationic polymer, such as, by way of example only, an oligopeptide (such as, by way of example only, between 5-20 amino acids) including at least one (and preferably multiple) Lys-Arg-Lys tripeptide sequence(s). In certain embodiments, the oligonucleotide is a deoxynucleotide

comprising 26-mer sequence 5'-$(IC)_{13}$-3'. In other embodiments, the polycationic polymer is a peptide comprising 11-mer amino acid sequence KLKLLLLLKLK.

[000363] In certain embodiments, bacterial ADP-ribosylating toxins and detoxified derivatives thereof are used as adjuvants in the immunogenic compositions described herein. In certain embodiments, such proteins are derived from E. coli (E. coli heat labile enterotoxin "LT"), cholera ("CT"), or pertussis ("PT"). In other embodiments, the toxin or toxoid is in the form of a holotoxin, comprising both A and B subunits. In other embodiments, the A subunit contains a detoxifying mutation; whereas the B subunit is not mutated. In other embodiments, the adjuvant is a detoxified LT mutant such as LT-K63, LT-R72, and LT-G192.

[000364] The human immunomodulators suitable for use as adjuvants include, but are not limited to, cytokines, such as, by way of example only, interleukins (IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12), interferons (such as, by way of example only, interferon-γ), macrophage colony stimulating factor, and tumor necrosis factor.

[000365] The bioadhesives and mucoadhesives used as adjuvants in the immunogenic compositions described herein include, but are not limited to, esterified hyaluronic acid microspheres, and cross-linked derivatives of poly(acrylic acid), polyvinyl alcohol, polyvinyl pyrollidone, polysaccharides and carboxymethylcellulose. In certain embodiments, chitosan and derivatives thereof are used as in the vaccine compositions described herein adjuvants.

[000366] The microparticles suitable for use as adjuvants include, but are not limited to, microparticles formed from materials that are biodegradable and non-toxic (e.g. a poly(.alpha.-hydroxy acid), a polyhydroxybutyric acid, a polyorthoester, a polyanhydride, a polycaprolactone, etc.), with poly(lactide-co-glycolide). In certain embodiments, such microparticles are treated to have a negatively-charged surface (e.g. with SDS) or a positively-charged surface (e.g. with a cationic detergent, such as CTAB). The microparticles suitable for use as adjuvants have a particle diameter of about.100 nm to about 150 μm in diameter. In certain embodiments, the particle diameter is about 200 nm to about 30 μm, and in other embodiments the particle diameter is about 500 nm to 10 μm.

[000367] The polyoxyethylene ether and polyoxyethylene ester formulations suitable for use as adjuvants include, but are not limited to, polyoxyethylene sorbitan ester surfactants in combination with an octoxynol, and polyoxyethylene alkyl ethers or ester surfactants in combination with at least one additional non-ionic surfactant such as an octoxynol. In certain embodiments, the polyoxyethylene ethers are selected from polyoxyethylene-9-lauryl ether (laureth 9),

polyoxyethylene-9-steoryl ether, polyoxytheylene-8-steoryl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether.

[000368] The muramyl peptides suitable for use as adjuvants include, but are not limited to, N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-normuramyl-L-alanyl-D-isoglutamine (nor-MDP), and N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-s- n-glycero-3-hydroxyphosphoryloxy)-ethylamine MTP-PE).

[000369] In certain embodiments, one or more compounds of Formula (I) used as an immune potentiator are included in compositions having combinations of one or more of the adjuvants identified above. Such combinations include, but are not limited to,

(1) a saponin and an oil-in-water emulsion;

(2) a saponin (e.g. QS21)+a non-toxic LPS derivative (e.g. 3dMPL);

(3) a saponin (e.g. QS21)+a non-toxic LPS derivative (e.g. 3dMPL)+a cholesterol;

(4) a saponin (e.g. QS21)+3dMPTL+IL-12 (optionally including a sterol);

(5) combinations of 3dMPL with, for example, QS21 and/or oil-in-water emulsions;

(6) SAF, containing 10% squalane, 0.4% Tween 80.TM., 5% pluronic-block polymer L121, and thr-MDP, either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion.

(7) RIBI™ adjuvant system (RAS), (Ribi Immunochem) containing 2% squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL+CWS (Detox.TM.); and

(8) one or more mineral salts (such as an aluminum salt)+a non-toxic derivative of LPS (such as 3dMPL).

[000370] In other embodiments, the adjuvant combinations used in the immunogenic combinations provided herein include combinations of Th1 and Th2 adjuvants such as, by way of example only, CpG and alum or resiquimod and alum.

[000371] In certain embodiments, the immunogenic compositions provided herein elicit both a cell mediated immune response as well as a humoral immune response. In other embodiments, the immune response induces long lasting (*e.g.* neutralising) antibodies and a cell mediated immunity that quickly responds upon exposure to the infectious agent.

[000372] Two types of T cells, CD4 and CD8 cells, are generally thought necessary to initiate and/or enhance cell mediated immunity and humoral immunity. CD8 T cells can express a CD8

co-receptor and are commonly referred to as Cytotoxic T lymphocytes (CTLs). CD8 T cells are able to recognized or interact with antigens displayed on MHC Class I molecules.

[000373] CD4 T cells can express a CD4 co-receptor and are commonly referred to as T helper cells. CD4 T cells are able to recognize antigenic peptides bound to MHC class II molecules. Upon interaction with a MHC class II molecule, the CD4 cells can secrete factors such as cytokines. These secreted cytokines can activate B cells, cytotoxic T cells, macrophages, and other cells that participate in an immune response. Helper T cells or CD4+ cells can be further divided into two functionally distinct subsets: TH1 phenotype and TH2 phenotypes which differ in their cytokine and effector function.

[000374] Activated TH1 cells enhance cellular immunity (including an increase in antigen-specific CTL production) and are therefore of particular value in responding to intracellular infections. Activated TH1 cells may secrete one or more of IL-2, IFN-γ, and TNF-β. A TH1 immune response may result in local inflammatory reactions by activating macrophages, NK (natural killer) cells, and CD8 cytotoxic T cells (CTLs). A TH1 immune response may also act to expand the immune response by stimulating growth of B and T cells with IL-12. TH1 stimulated B cells may secrete IgG2a.

[000375] Activated TH2 cells enhance antibody production and are therefore of value in responding to extracellular infections. Activated TH2 cells may secrete one or more of IL-4, IL-5, IL-6, and IL-10. A TH2 immune response may result in the production of IgG1, IgE, IgA and memory B cells for future protection.

[000376] An enhanced immune response may include one or more of an enhanced TH1 immune response and a TH2 immune response.

[000377] A TH1 immune response may include one or more of an increase in CTLs, an increase in one or more of the cytokines associated with a TH1 immune response (such as IL-2, IFN-γ, and TNF-β), an increase in activated macrophages, an increase in NK activity, or an increase in the production of IgG2a. Preferably, the enhanced TH1 immune response will include an increase in IgG2a production.

[000378] TH1 adjuvants can be used to elicit a TH1 immune response. A TH1 adjuvant will generally elicit increased levels of IgG2a production relative to immunization of the antigen without adjuvant. TH1 adjuvants suitable for use in immunogenic compositions provided herein include, but are not limited to, saponin formulations, virosomes and virus like particles, non-toxic derivatives of enterobacterial lipopolysaccharide (LPS), immunostimulatory oligonucleotides. In

certain embodiments, the immunostimulatory oligonucleotides used as TH1 adjuvants in the immunogenic compositions provided herein contain a CpG motif.

[000379] A TH2 immune response may include one or more of an increase in one or more of the cytokines associated with a TH2 immune response (such as IL-4, IL-5, IL-6 and IL-10), or an increase in the production of IgG1, IgE, IgA and memory B cells. Preferably, the enhanced TH2 immune response will include an increase in IgG1 production.

[000380] TH2 adjuvants can be used to elicit a TH2 immune response. A TH2 adjuvant will generally elicit increased levels of IgG1 production relative to immunization of the antigen without adjuvant. TH2 adjuvants suitable for use in immunogenic compositions provided herein include, but are not limited to, mineral containing compositions, oil-emulsions, and ADP-ribosylating toxins and detoxified derivatives thereof. In certain embodiments, the mineral containing compositions used as TH2 adjuvants in the immunogenic compositions provided herein are aluminium salts.

[000381] In certain embodiments, the immunogenic compositions provided herein include a TH1 adjuvant and a TH2 adjuvant. In other embodiments, such compositions elicit an enhanced TH1 and an enhanced TH2 response, such as, an increase in the production of both IgG1 and IgG2a production relative to immunization without an adjuvant. In still other embodiments, such compositions comprising a combination of a TH1 and a TH2 adjuvant elicit an increased TH1 and/or an increased TH2 immune response relative to immunization with a single adjuvant (i.e., relative to immunization with a TH1 adjuvant alone or immunization with a TH2 adjuvant alone).

[000382] In certain embodiments, the immune response is one or both of a TH1 immune response and a TH2 response. In other embodiments, the immune response provides for one or both of an enhanced TH1 response and an enhanced TH2 response.

[000383] In certain embodiments, the enhanced immune response is one or both of a systemic and a mucosal immune response. In other embodiments, the immune response provides for one or both of an enhanced systemic and an enhanced mucosal immune response. In certain embodiments, the mucosal immune response is a TH2 immune response. In certain embodiments, the mucosal immune response includes an increase in the production of IgA.

[000384] In certain embodiments the immunogenic compositions provided herein are used as vaccines, wherein such compositions include an immunologically effective amount of one or more antigen).

[000385] Antigens for use with the immunogenic compositions provided herein include, but are

not limited to, one or more of the following antigens set forth below, or antigens derived from one or more of the pathogens set forth below.

Bacterial Antigens

[000386] Bacterial antigens suitable for use in immunogenic compositions provided herein include, but are not limited to, proteins, polysaccharides, lipopolysaccharides, and outer membrane vesicles which are isolated, purified or derived from a bacteria. In certain embodiments, the bacterial antigens include bacterial lysates and inactivated bacteria formulations. In certain embodiments, the bacterial antigens are produced by recombinant expression. In certain embodiments, the bacterial antigens include epitopes which are exposed on the surface of the bacteria during at least one stage of its life cycle. Bacterial antigens are preferably conserved across multiple serotypes. In certain embodiments, the bacterial antigens include antigens derived from one or more of the bacteria set forth below as well as the specific antigens examples identified below:

Neisseria meningitidis: Meningitidis antigens include, but are not limited to, proteins, saccharides (including a polysaccharide, oligosaccharide, lipooligosaccharide or lipopolysaccharide), or outer-membrane vesicles purified or derived from *N. meningitides* serogroup such as A, C, W135, Y, X and/or B. In certain embodiments meningitides protein antigens are be selected from adhesions, autotransporters, toxins, Fe acquisition proteins, and membrane associated proteins (preferably integral outer membrane protein).

Streptococcus pneumoniae: *Streptococcus pneumoniae* antigens include, but are not limited to, a saccharide (including a polysaccharide or an oligosaccharide) and/or protein from *Streptococcus pneumoniae*. The saccharide may be a polysaccharide having the size that arises during purification of the saccharide from bacteria, or it may be an oligosaccharide achieved by fragmentation of such a polysaccharide. In the 7-valent PREVNAR™ product, for instance, 6 of the saccharides are presented as intact polysaccharides while one (the 18C serotype) is presented as an oligosaccharide. In certain embodiments saccharide antigens are selected from one or more of the following pneumococcal serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and/or 33F. An immunogenic composition may include multiple serotypes *e.g.* 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or more serotypes. 7-valent, 9-valent, 10-valent,

11-valent and 13-valent conjugate combinations are already known in the art, as is a 23-valent unconjugated combination. For example, an 10-valent combination may include saccharide from serotypes 1 , 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. An 11-valent combination may further include saccharide from serotype 3. A 12-valent combination may add to the 10-valent mixture: serotypes 6A and 19A; 6A and 22F; 19A and 22F; 6A and 15B; 19A and 15B; r 22F and 15B; A 13-valent combination may add to the 11-valent mixture: serotypes 19A and 22F; 8 and 12F; 8 and 15B; 8 and 19A; 8 and 22F; 12F and 15B; 12F and 19A; 12F and 22F; 15B and 19A; 15B and 22F. *etc.* In certain embodiments, protein antigens may be selected from a protein identified in WO98/18931, WO98/18930, US Patent 6,699,703, US Patent 6,800,744, WO97/43303, WO97/37026, WO 02/079241, WO 02/34773, WO 00/06737, WO 00/06738, WO 00/58475, WO 2003/082183, WO 00/37105, WO 02/22167, WO 02/22168, WO 2003/104272, WO 02/08426, WO 01/12219, WO 99/53940, WO 01/81380, WO 2004/092209, WO 00/76540, WO 2007/116322, LeMieux *et al.*, Infect. Imm. (2006) 74:2453-2456, Hoskins *et al.*, J. Bacteriol. (2001) 183:5709-5717, Adamou *et al.*, Infect. Immun. (2001) 69(2):949-958, Briles *et al.*, J. Infect. Dis. (2000) 182:1694-1701, Talkington *et al.*, Microb. Pathog. (1996) 21(1):17-22, Bethe *et al.*, FEMS Microbiol. Lett. (2001) 205(1):99-104, Brown *et al.*, Infect. Immun. (2001) 69:6702-6706, Whalen *et al.*, FEMS Immunol. Med. Microbiol. (2005) 43:73-80, Jomaa *et al.*, Vaccine (2006) 24(24):5133-5139. In other embodiments, *Streptococcus pneumoniae* proteins may be selected from the Poly Histidine Triad family (PhtX), the Choline Binding Protein family (CbpX), CbpX truncates, LytX family, LytX truncates, CbpX truncate-LytX truncate chimeric proteins, pneumolysin (Ply), PspA, PsaA, Spl28, SpIOl, Spl30, Spl25, Spl33, pneumococcal pilus subunits.

Streptococcus pyogenes (Group A Streptococcus): Group A Streptococcus antigens include, but are not limited to, a protein identified in WO 02/34771 or WO 2005/032582 (including GAS 40), fusions of fragments of GAS M proteins (including those described in WO 02/094851, and Dale, Vaccine (1999) 17:193-200, and Dale, Vaccine 14(10): 944-948), fibronectin binding protein (Sfb1), Streptococcal heme-associated protein (Shp), and Streptolysin S (SagA).

Moraxella catarrhalis: Moraxella antigens include, but are not limited to, antigens identified in WO 02/18595 and WO 99/58562, outer membrane protein antigens (HMW-OMP), C-antigen, and/or LPS.

Bordetella pertussis: Pertussis antigens include, but are not limited to, pertussis holotoxin (PT) and filamentous haemagglutinin (FHA) from *B. pertussis*, optionally also combination with pertactin and/or agglutinogens 2 and 3.

Burkholderia: Burkholderia antigens include, but are not limited to *Burkholderia mallei*, *Burkholderia pseudomallei* and *Burkholderia cepacia.*

Staphylococcus aureus: Staph aureus antigens include, but are not limited to, a polysaccharide and/or protein from *S. aureus*. *S. aureus* polysaccharides include, but are not limited to, type 5 and type 8 capsular polysaccharides (CP5 and CP8) optionally conjugated to nontoxic recombinant *Pseudomonas aeruginosa* exotoxin A, such as StaphVAX™, type 336 polysaccharides (336PS), polysaccharide intercellular adhesions (PIA, also known as PNAG). *S. aureus* proteins include, but are not limited to, antigens derived from surface proteins, invasins (leukocidin, kinases, hyaluronidase), surface factors that inhibit phagocytic engulfment (capsule, Protein A), carotenoids, catalase production, Protein A, coagulase, clotting factor, and/or membrane-damaging toxins (optionally detoxified) that lyse eukaryotic cell membranes (hemolysins, leukotoxin, leukocidin). In certain embodiments, *S. aureus* antigens may be selected from a protein identified in WO 02/094868, WO 2008/019162, WO 02/059148, WO 02/102829, WO 03/011899, WO 2005/079315, WO 02/077183, WO 99/27109, WO 01/70955, WO 00/12689, WO 00/12131, WO 2006/032475, WO 2006/032472, WO 2006/032500, WO 2007/113222, WO 2007/113223, WO 2007/113224. In other embodiments, *S. aureus* antigens may be selected from IsdA, IsdB, IsdC, SdrC, SdrD, SdrE, ClfA, ClfB, SasF, SasD, SasH (AdsA), Spa, EsaC, EsxA, EsxB, Emp, HlaH35L, CP5, CP8, PNAG, 336PS.

Staphylococcus epidermis: S. epidermidis antigens include, but are not limited to, slime-associated antigen (SAA).

Clostridium tetani (Tetanus): Tetanus antigens include, but are not limited to, tetanus toxoid (TT). In certain embodiments such antigens are used as a carrier protein in conjunction/conjugated with the immunogenic compositions provided herein.

Clostridium perfringens: Antigens include, but are not limited to, Epsilon toxin from *Clostridium perfringen.*

Clostridium botulinums (Botulism): Botulism antigens include, but are not limited to, those derived from *C. botulinum.*

Cornynebacterium diphtheriae (Diphtheria): Diphtheria antigens include, but are not limited to, diphtheria toxin, preferably detoxified, such as CRM_{197}. Additionally antigens capable of modulating, inhibiting or associated with ADP ribosylation are contemplated for combination/co-administration/conjugation with the immunogenic compositions provided herein. In certain embodiments, the diphtheria toxoids are used as carrier proteins.

Haemophilus influenzae B (Hib): Hib antigens include, but are not limited to, a Hib saccharide antigen.

Pseudomonas aeruginosa: Pseudomonas antigens include, but are not limited to, endotoxin A, Wzz protein, *P. aeruginosa* LPS, LPS isolated from PAO1 (O5 serotype), and/or Outer Membrane Proteins, including Outer Membrane Proteins F (OprF).

Legionella pneumophila. Bacterial antigens derived from Legionella pneumophila.

Coxiella burnetii. Bacterial antigens derived from Coxiella burnetii.

Brucella. Bacterial antigens derived from Brucella, including but not limited to, *B. abortus, B. canis, B. melitensis, B. neotomae, B. ovis, B. suis and B. pinnipediae.*

Francisella. Bacterial antigens derived from Francisella, including but not limited to, *F. novicida, F. philomiragia* and *F. tularensis.*

Streptococcus agalactiae (Group B Streptococcus): Group B Streptococcus antigens include, but are not limited to, a protein or saccharide antigen identified in WO 02/34771, WO 03/093306, WO 04/041157, or WO 2005/002619 (including proteins GBS 80, GBS 104, GBS 276 and GBS 322, and including saccharide antigens derived from serotypes Ia, Ib, Ia/c, II, III, IV, V, VI, VII and VIII).

Neiserria gonorrhoeae: Gonorrhoeae antigens include,but are not limited to, Por (or porin) protein, such as PorB (see Zhu *et al.*, *Vaccine* (2004) 22:660 - 669), a transferring binding protein, such as TbpA and TbpB (See Price *et al.*, Infection and Immunity (2004) 71(1):277 - 283), a opacity protein (such as Opa), a reduction-modifiable protein (Rmp), and outer membrane vesicle (OMV) preparations (see Plante *et al*, J

Infectious Disease (2000) 182:848 - 855), also see, *e.g.*, WO99/24578, WO99/36544, WO99/57280, WO02/079243)..

Chlamydia trachomatis: Chlamydia trachomatis antigens include, but are not limited to, antigens derived from serotypes A, B, Ba and C (agents of trachoma, a cause of blindness), serotypes L_1, L_2 & L_3 (associated with Lymphogranuloma venereum), and serotypes, D-K. In certain embodiments, chlamydia trachomas antigens include, but are not limited to, an antigen identified in WO 00/37494, WO 03/049762, WO 03/068811, or WO 05/002619, including PepA (CT045), LcrE (CT089), ArtJ (CT381), DnaK (CT396), CT398, OmpH-like (CT242), L7/L12 (CT316), OmcA (CT444), AtosS (CT467), CT547, Eno (CT587), HrtA (CT823), and MurG (CT761).

Treponema pallidum (Syphilis): Syphilis antigens include, but are not limited to, TmpA antigen.

Haemophilus ducreyi (causing chancroid): Ducreyi antigens include, but are not limited to, outer membrane protein (DsrA).

Enterococcus faecalis or Enterococcus faecium: Antigens include, but are not limited to, a trisaccharide repeat or other *Enterococcus* derived antigens.

Helicobacter pylori: H pylori antigens include, but are not limited to, Cag, Vac, Nap, HopX, HopY and/or urease antigen.

Staphylococcus saprophyticus: Antigens include, but are not limited to, the 160 kDa hemagglutinin of *S. saprophyticus* antigen.

Yersinia enterocolitica Antigens include, but are not limited to, LPS.

E. coli: E. coli antigens may be derived from enterotoxigenic *E. coli* (ETEC), enteroaggregative *E. coli* (EAggEC), diffusely adhering *E. coli* (DAEC), enteropathogenic *E. coli* (EPEC), extraintestinal pathogenic *E. coli* (ExPEC) and/or enterohemorrhagic *E. coli* (EHEC). ExPEC antigens include, but are not limited to, accessory colonization factor (orf3526), orf353, bacterial Ig-like domain (group 1) protein (orf405), orf1364, NodT-family outer-membrane-factor-lipoprotein efflux transporter (orf1767), gspK (orf3515), gspJ (orf3516), tonB-dependent siderophore receptor (orf3597), fimbrial protein (orf3613), upec-948, upec-1232, A chain precursor of the type-1 fimbrial protein (upec-1875), yap H homolog (upec-2820), and hemolysin A (recp-3768).

Bacillus anthracis (anthrax)*: B. anthracis* antigens include, but are not limited to, A-components (lethal factor (LF) and edema factor (EF)), both of which can share a common B-component known as protective antigen (PA). In certain embodiments, *B. anthracis* antigens are optionally detoxified.

Yersinia pestis (plague): Plague antigens include, but are not limited to, F1 capsular antigen, LPS, Yersinia pestis V antigen.

Mycobacterium tuberculosis: Tuberculosis antigens include, but are not limited to, lipoproteins, LPS, BCG antigens, a fusion protein of antigen 85B (Ag85B), ESAT-6 optionally formulated in cationic lipid vesicles, Mycobacterium tuberculosis (Mtb) isocitrate dehydrogenase associated antigens, and MPT51 antigens.

Rickettsia: Antigens include, but are not limited to, outer membrane proteins, including the outer membrane protein A and/or B (OmpB), LPS, and surface protein antigen (SPA).

Listeria monocytogenes: Bacterial antigens include, but are not limited to, those derived from Listeria monocytogenes.

Chlamydia pneumoniae: Antigens include, but are not limited to, those identified in WO 02/02606.

Vibrio cholerae: Antigens include, but are not limited to, proteinase antigens, LPS, particularly lipopolysaccharides of Vibrio cholerae II, O1 Inaba O-specific polysaccharides, V. cholera O139, antigens of IEM108 vaccine and Zonula occludens toxin (Zot).

Salmonella typhi (typhoid fever): Antigens include, but are not limited to, capsular polysaccharides preferably conjugates (Vi, i.e. vax-TyVi).

Borrelia burgdorferi (Lyme disease): Antigens include, but are not limited to, lipoproteins (such as OspA, OspB, Osp C and Osp D), other surface proteins such as OspE-related proteins (Erps), decorin-binding proteins (such as DbpA), and antigenically variable VI proteins, such as antigens associated with P39 and P13 (an integral membrane protein, VlsE Antigenic Variation Protein.

Porphyromonas gingivalis: Antigens include, but are not limited to, *P. gingivalis* outer membrane protein (OMP).

Klebsiella: Antigens include, but are not limited to, an OMP, including OMP A, or a polysaccharide optionally conjugated to tetanus toxoid.

[000387] Other bacterial antigens used in the immunogenic compositions provided herein

include, but are not limited to, capsular antigens, polysaccharide antigens or protein antigens of any of the above. Other bacterial antigens used in the immunogenic compositions provided herein include, but are not limited to, an outer membrane vesicle (OMV) preparation. Additionally, Other bacterial antigens used in the immunogenic compositions provided herein include, but are not limited to, live, attenuated, and/or purified versions of any of the aforementioned bacteria. In certain embodiments, the bacterial antigens used in the immunogenic compositions provided herein are derived from gram-negative, while in other embodiments they are derived from gram-positive bacteria. In certain embodiments, the bacterial antigens used in the immunogenic compositions provided herein are derived from aerobic bacteria, while in other embodiments they are derived from anaerobic bacteria.

[000388] In certain embodiments, any of the above bacterial-derived saccharides (polysaccharides, LPS, LOS or oligosaccharides) are conjugated to another agent or antigen, such as a carrier protein (for example CRM_{197}). In certain embodiments, such conjugations are direct conjugations effected by reductive amination of carbonyl moieties on the saccharide to amino groups on the protein. In other embodiments, the saccharides are conjugated through a linker, such as, with succinamide or other linkages provided in *Bioconjugate Techniques,* 1996 and *CRC, Chemistry of Protein Conjugation and Cross-Linking*, 1993.

[000389] In certain embodiments useful for the treatment or prevention of *Neisseria* infection and related diseases and disorders, recombinant proteins from *N. meningitidis* for use in the immunogenic compositions provided herein may be found in WO99/24578, WO99/36544, WO99/57280, WO00/22430, WO96/29412, WO01/64920, WO03/020756, WO2004/048404, and WO2004/032958. Such antigens may be used alone or in combinations. Where multiple purified proteins are combined then it is helpful to use a mixture of 10 or fewer (e.g. 9, 8, 7, 6, 5, 4, 3, 2) purified antigens.

[000390] A particularly useful combination of antigens for use in the immunogenic compositions provided herein is disclosed in Giuliani *et al.* (2006) *Proc Natl Acad Sci U S A* 103(29):10834-9 and WO2004/032958, and so an immunogenic composition may include 1, 2, 3, 4 or 5 of: (1) a 'NadA' protein (aka GNA1994 and NMB1994); (2) a 'fHBP' protein (aka '741', LP2086, GNA1870, and NMB1870); (3) a '936' protein (aka GNA2091 and NMB2091); (4) a '953' protein (aka GNA1030 and NMB1030); and (5) a '287' protein (aka GNA2132 and NMB2132). Other possible antigen combinations may comprise a transferrin binding protein (e.g. TbpA and/or TbpB) and an Hsf antigen. Other possible purified antigens for use in the immunogenic

compositions provided herein include proteins comprising one of the following amino acid sequences: SEQ ID NO:650 from WO99/24578; SEQ ID NO:878 from WO99/24578; SEQ ID NO:884 from WO99/24578; SEQ ID NO:4 from WO99/36544; SEQ ID NO:598 from WO99/57280; SEQ ID NO:818 from WO99/57280; SEQ ID NO:864 from WO99/57280; SEQ ID NO:866 from WO99/57280; SEQ ID NO:1196 from WO99/57280; SEQ ID NO:1272 from WO99/57280; SEQ ID NO:1274 from WO99/57280; SEQ ID NO:1640 from WO99/57280; SEQ ID NO:1788 from WO99/57280; SEQ ID NO:2288 from WO99/57280; SEQ ID NO:2466 from WO99/57280; SEQ ID NO:2554 from WO99/57280; SEQ ID NO:2576 from WO99/57280; SEQ ID NO:2606 from WO99/57280; SEQ ID NO:2608 from WO99/57280; SEQ ID NO:2616 from WO99/57280; SEQ ID NO:2668 from WO99/57280; SEQ ID NO:2780 from WO99/57280; SEQ ID NO:2932 from WO99/57280; SEQ ID NO:2958 from WO99/57280; SEQ ID NO:2970 from WO99/57280; SEQ ID NO:2988 from WO99/57280 (each of the forgoing amino acid sequences is hereby incorporated by reference from the cited document), or a polypeptide comprising an amino acid sequence which: (a) has 50% or more identity (*e.g.*, 60%, 70%, 80%, 90%, 95%, 99% or more) to said sequences; and/or (b) comprises a fragment of at least n consecutive amino acids from said sequences, wherein n is 7 or more (*e.g.*, 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). Preferred fragments for (b) comprise an epitope from the relevant sequence. More than one (*e.g.*, 2, 3, 4, 5, 6) of these polypeptides may be included in the immunogenic compositions.

[000391] The fHBP antigen falls into three distinct variants (WO2004/048404). An *N. meningitidis* serogroup vaccine based upon the immunogenic compositions disclosed herein utilizing one of the compounds disclosed herein may include a single fHBP variant, but is will usefully include an fHBP from each of two or all three variants. Thus the immunogenic composition may include a combination of two or three different purified fHBPs, selected from: (a) a first protein, comprising an amino acid sequence having at least a% sequence identity to SEQ ID NO: 1 and/or comprising an amino acid sequence consisting of a fragment of at least x contiguous amino acids from SEQ ID NO: 1; (b) a second protein, comprising an amino acid sequence having at least b% sequence identity to SEQ ID NO: 2 and/or comprising an amino acid sequence consisting of a fragment of at least y contiguous amino acids from SEQ ID NO: 2; and/or (c) a third protein, comprising an amino acid sequence having at least c% sequence identity to SEQ ID NO: 3 and/or comprising an amino acid sequence consisting of a fragment of at least z contiguous amino acids from SEQ ID NO: 3

[000392] SEQ ID NO: 1

VAADIGAGLADALTAPLDHKDKGLQSLTLDQSVRKNEKLKLAAQGAEKTYGNGDSLNT GKLKNDKVSRFDFIRQIEVDGQLITLESGEFQVYKQSHSALTAFQTEQIQDSEHSGKMVAK RQFRIGDIAGEHTSFDKLPEGGRATYRGTAFGSDDAGGKLTYTIDFAAKQGNGKIEHLKSP ELNVDLAAADIKPDGKRHAVISGSVLYNQAEKGSYSLGIFGGKAQEVAGSAEVKTVNGIR HIGLAAKQ

[000393] SEQ ID NO: 2

VAADIGAGLADALTAPLDHKDKSLQSLTLDQSVRKNEKLKLAAQGAEKTYGNGDSLNTG KLKNDKVSRFDFIRQIEVDGQLITLESGEFQIYKQDHSAVVALQIEKINNPDKIDSLINQRSF LVSGLGGEHTAFNQLPDGKAEYHGKAFSSDDAGGKLTYTIDFAAKQGHGKIEHLKTPEQ NVELAAAELKADEKSHAVILGDTRYGSEEKGTYHLALFGDRAQEIAGSATVKIGEKVHEI GIAGKQ

[000394] SEQ ID NO: 3

VAADIGTGLADALTAPLDHKDKGLKSLTLEDSIPQNGTLTLSAQGAEKTFKAGDKDNSLN TGKLKNDKISRFDFVQKIEVDGQTITLASGEFQIYKQNHSAVVALQIEKINNPDKTDSLINQ RSFLVSGLGGEHTAFNQLPGGKAEYHGKAFSSDDPNGRLHYSIDFTKKQGYGRIEHLKTL EQNVELAAAELKADEKSHAVILGDTRYGSEEKGTYHLALFGDRAQEIAGSATVKIGEKVH EIGIAGKQ.

[000395] The value of a is at least 85, *e.g.*, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, or more. The value of b is at least 85, *e.g.*, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, or more. The value of c is at least 85, *e.g.*, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, or more. The values of a, b and c are not intrinsically related to each other.

[000396] The value of x is at least 7, *e.g.*, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 225, 250). The value of y is at least 7, *e.g.*, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 225, 250). The value of z is at least 7, *e.g.*, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 225, 250). The values of x, y and z are not intrinsically related to each other.

[000397] In some embodiments, the immunogenic compositions as disclosed herein will include fHBP protein(s) that are lipidated, *e.g.*, at a N-terminal cysteine. In other embodiments they will

not be lipidated

[000398] A useful immunogenic composition as disclosed herein includes purified proteins comprises a mixture of: (i) a first polypeptide having amino acid sequence SEQ ID NO: 4; (ii) a second polypeptide having amino acid sequence SEQ ID NO: 5; and (iii) a third polypeptide having amino acid sequence SEQ ID NO: 6. See Giuliani *et al.* (2006) *Proc Natl Acad Sci U S A* 103(29):10834-9 and WO2004/032958. A useful immunogenic composition as disclosed herein includes purified proteins comprises a mixture of: (i) a first polypeptide having at least a% sequence identity to amino acid sequence SEQ ID NO: 4; (ii) a second polypeptide having at least b% sequence identity to amino acid sequence SEQ ID NO: 5; and (iii) a third polypeptide having at least a% sequence identity to amino acid sequence SEQ ID NO: 6.

[000399] SEQ ID NO: 4

MASPDVKSADTLSKPAAPVVSEKETEAKEDAPQAGSQGQGAPSAQGGQDMAAVSEENT
GNGGAAATDKPKNEDEGAQNDMPQNAADTDSLTPNHTPASNMPAGNMENQAPDAGES
EQPANQPDMANTADGMQGDDPSAGGENAGNTAAQGTNQAENNQTAGSQNPASSTNPSA
TNSGGDFGRTNVGNSVVIDGPSQNITLTHCKGDSCSGNNFLDEEVQLKSEFEKLSDADKIS
NYKKDGKNDGKNDKFVGLVADSVQMKGINQYIIFYKPKPTSFARFRRSARSRRSLPAEMP
LIPVNQADTLIVDGEAVSLTGHSGNIFAPEGNYRYLTYGAEKLPGGSYALRVQGEPSKGE
MLAGTAVYNGEVLHFHTENGRPSPSRGRFAAKVDFGSKSVDGIIDSGDGLHMGTQKFKA
AIDGNGFKGTWTENGGGDVSGKFYGPAGEEVAGKYSYRPTDAEKGGFGVFAGKKEQDG
SGGGGATYKVDEYHANARFAIDHFNTSTNVGGFYGLTGSVEFDQAKRDGKIDITIPVANL
QSGSQHFTDHLKSADIFDAAQYPDIRFVSTKFNFNGKKLVSVDGNLTMHGKTAPVKLKAE
KFNCYQSPMAKTEVCGGDFSTTIDRTKWGVDYLVNVGMTKSVRIDIQIEAAKQ

[000400] SEQ ID NO: 5

MVSAVIGSAAVGAKSAVDRRTTGAQTDDNVMALRIETTARSYLRQNNQTKGYTPQISVV
GYNRHLLLLGQVATEGEKQFVGQIARSEQAAEGVYNYITVASLPRTAGDIAGDTWNTSK
VRATLLGISPATQARVKIVTYGNVTYVMGILTPEEQAQITQKVSTTVGVQKVITLYQNYV
QRGSGGGGVAADIGAGLADALTAPLDHKDKGLQSLTLDQSVRKNEKLKLAAQGAEKTY
GNGDSLNTGKLKNDKVSRFDFIRQIEVDGQLITLESGEFQVYKQSHSALTAFQTEQIQDSE
HSGKMVAKRQFRIGDIAGEHTSFDKLPEGGRATYRGTAFGSDDAGGKLTYTIDFAAKQG
NGKIEHLKSPELNVDLAAADIKPDGKRHAVISGSVLYNQAEKGSYSLGIFGGKAQEVAGS
AEVKTVNGIRHIGLAAKQ

[000401] SEQ ID NO: 6

ATNDDDVKKAATVAIAAAYNNGQEINGFKAGETIYDIDEDGTITKKDATAADVEADDFK
GLGLKKVVTNLTKTVNENKQNVDAKVKAAESEIEKLTTKLADTDAALADTDAALDATT
NALNKLGENITTFAEETKTNIVKIDEKLEAVADTVDKHAEAFNDIADSLDETNTKADEAV
KTANEAKQTAEETKQNVDAKVKAAETAAGKAEAAAGTANTAADKAEAVAAKVTDIKA
DIATNKDNIAKKANSADVYTREESDSKFVRIDGLNATTEKLDTRLASAEKSIADHDTRLN
GLDKTVSDLRKETRQGLAEQAALSGLFQPYNVG.

Bacterial Vesicle Antigens

[000402] The immunogenic compositions as disclosed herein may include outer membrane vesicles. Such outer membrane vesicles may be obtained from a wide array of pathogenic bacteria and used as antigenic components of the immunogenic compositions as disclosed herein. Vesicles for use as antigenic components of such immunogenic compositions include any proteoliposomic vesicle obtained by disrupting a bacterial outer membrane to form vesicles therefrom that include protein components of the outer membrane. Thus the term includes OMVs (sometimes referred to as 'blebs'), microvesicles (MVs, see, *e.g.*, WO02/09643) and 'native OMVs' ('NOMVs' see, *e.g.*, Katial *et al.* (2002) *Infect. Immun.* 70:702-707). Immnogenic compositions as disclosed herein that include vesicles from one or more pathogenic bacteria can be used in the treatment or prevention of infection by such pathogenic bacteria and related diseases and disorders.

[000403] MVs and NOMVs are naturally-occurring membrane vesicles that form spontaneously during bacterial growth and are released into culture medium. MVs can be obtained by culturing bacteria such as *Neisseria* in broth culture medium, separating whole cells from the smaller MVs in the broth culture medium (*e.g.*, by filtration or by low-speed centrifugation to pellet only the cells and not the smaller vesicles), and then collecting the MVs from the cell-depleted medium (*e.g.*, by filtration, by differential precipitation or aggregation of MVs, by high-speed centrifugation to pellet the MVs). Strains for use in production of MVs can generally be selected on the basis of the amount of MVs produced in culture (see, *e.g.*, US patent 6,180,111 and WO01/34642 describing *Neisseria* with high MV production).

[000404] OMVs are prepared artificially from bacteria, and may be prepared using detergent treatment (*e.g.*, with deoxycholate), or by non detergent means (see, *e.g.*, WO04/019977). Methods for obtaining suitable OMV preparations are well known in the art. Techniques for forming OMVs include treating bacteria with a bile acid salt detergent (*e.g.*, salts of lithocholic acid, chenodeoxycholic acid, ursodeoxycholic acid, deoxycholic acid, cholic acid, ursocholic acid, etc.,

with sodium deoxycholate (EP0011243 and Fredriksen *et al.* (1991) *NIPH Ann.* 14(2):67-80) being preferred for treating Neisseria) at a pH sufficiently high not to precipitate the detergent (see, *e.g.*, WO01/91788). Other techniques may be performed substantially in the absence of detergent (see, *e.g.*, WO04/019977) using techniques such as sonication, homogenisation, microfluidisation, cavitation, osmotic shock, grinding, French press, blending, etc. Methods using no or low detergent can retain useful antigens such as NspA in *Neisserial* OMVs. Thus a method may use an OMV extraction buffer with about 0.5% deoxycholate or lower, *e.g.*, about 0.2%, about 0.1%, <0.05% or zero.

[000405] A useful process for OMV preparation is described in WO05/004908 and involves ultrafiltration on crude OMVs, rather than instead of high speed centrifugation. The process may involve a step of ultracentrifugation after the ultrafiltration takes place.

[000406] Vesicles can be prepared from any pathogenic strain such as *Neisseria minigtidis* for use with the invention. Vessicles from *Neisserial meningitidis* serogroup B may be of any serotype (*e.g.*, 1, 2a, 2b, 4, 14, 15, 16, etc.), any serosubtype, and any immunotype (*e.g.*, L1; L2; L3; L3,3,7; L10; etc.). The meningococci may be from any suitable lineage, including hyperinvasive and hypervirulent lineages, *e.g.*, any of the following seven hypervirulent lineages: subgroup I; subgroup III; subgroup IV 1; ET 5 complex; ET 37 complex; A4 cluster; lineage 3. These lineages have been defined by multilocus enzyme electrophoresis (MLEE), but multilocus sequence typing (MLST) has also been used to classify meningococci, *e.g.*, the ET 37 complex is the ST 11 complex by MLST, the ET 5 complex is ST-32 (ET-5), lineage 3 is ST 41/44, etc. Vesicles can be prepared from strains having one of the following subtypes: P1.2; P1.2,5; P1.4; P1.5; P1.5,2; P1.5,c; P1.5c,10; P1.7,16; P1.7,16b; P1.7h,4; P1.9; P1.15; P1.9,15; P1.12,13; P1.13; P1.14; P1.21,16; P1.22,14.

[000407] Vesicles included in the immunogenic compositions disclosed herein may be prepared from wild type pathogenic strains such as *N. meningitidis* strains or from mutant strains. By way of example, WO98/56901 discloses preparations of vesicles obtained from *N.meningitidis* with a modified *fur* gene. WO02/09746 teaches that *nspA* expression should be up regulated with concomitant *porA* and *cps* knockout. Further knockout mutants of N.meningitidis for OMV production are disclosed in WO02/0974, WO02/062378, and WO04/014417. WO06/081259 discloses vesicles in which *fHBP* is upregulated. Claassen *et al.* (1996) 14(10):1001-8, disclose the construction of vesicles from strains modified to express six different *PorA* subtypes. Mutant *Neisseria* with low endotoxin levels, achieved by knockout of enzymes involved in LPS

biosynthesis, may also be used (see, *e.g.*, WO99/10497 and Steeghs *et al.* (2001) i20:6937-6945). These or others mutants can all be used with the invention.

[000408] Thus *N. meningitidis* serogroup B strains included in the immunogenic compositions disclosed herein may in some embodiments express more than one *PorA* subtype. Six valent and nine valent *PorA* strains have previously been constructed. The strain may express 2, 3, 4, 5, 6, 7, 8 or 9 of *PorA* subtypes: P1.7,16; P1.5-1,2-2; P1.19,15-1; P1.5-2,10; P1.12 1,13; P1.7-2,4; P1.22,14; P1.7-1,1 and/or P1.18-1,3,6. In other embodiments a strain may have been down regulated for *PorA* expression, *e.g.*, in which the amount of *PorA* has been reduced by at least 20% (*e.g.*, >30%, >40%, >50%, >60%, >70%, >80%, >90%, >95%, etc.), or even knocked out, relative to wild type levels (*e.g.*, relative to strain H44/76, as disclosed in WO03/105890).

[000409] In some embodiments *N. meningitidis* serogroup B strains may over express (relative to the corresponding wild-type strain) certain proteins. For instance, strains may over express NspA, protein 287 (WO01/52885 – also referred to as NMB2132 and GNA2132), one or more fHBP (WO06/081259 and U.S. Pat. Pub. 2008/0248065 - also referred to as protein 741, NMB1870 and GNA1870), TbpA and/or TbpB (WO00/25811), Cu,Zn-superoxide dismutase (WO00/25811), etc.

[000410] In some embodiments *N. meningitidis* serogroup B strains may include one or more of the knockout and/or over expression mutations. Preferred genes for down regulation and/or knockout include: (a) Cps, CtrA, CtrB, CtrC, CtrD, FrpB, GalE, HtrB/MsbB, LbpA, LbpB, LpxK, Opa, Opc, PilC, PorB, SiaA, SiaB, SiaC, SiaD, TbpA, and/or TbpB (WO01/09350); (b) CtrA, CtrB, CtrC, CtrD, FrpB, GalE, HtrB/MsbB, LbpA, LbpB, LpxK, Opa, Opc, PhoP, PilC, PmrE, PmrF, SiaA, SiaB, SiaC, SiaD, TbpA, and/or TbpB (WO02/09746); (c) ExbB, ExbD, rmpM, CtrA, CtrB, CtrD, GalE, LbpA, LpbB, Opa, Opc, PilC, PorB, SiaA, SiaB, SiaC, SiaD, TbpA, and/or TbpB (WO02/062378); and (d) CtrA, CtrB, CtrD, FrpB, OpA, OpC, PilC, PorB, SiaD, SynA, SynB, and/or SynC (WO04/014417).

[000411] Where a mutant strain is used, in some embodiments it may have one or more, or all, of the following characteristics: (i) down regulated or knocked-out LgtB and/or GalE to truncate the meningococcal LOS; (ii) up regulated TbpA; (iii) up regulated Hsf; (iv) up regulated Omp85; (v) up regulated LbpA; (vi) up regulated NspA; (vii) knocked-out PorA; (viii) down regulated or knocked-out FrpB; (ix) down regulated or knocked-out Opa; (x) down regulated or knocked-out Opc; (xii) deleted cps gene complex. A truncated LOS can be one that does not include a sialyl-lacto-N-neotetraose epitope, *e.g.*, it might be a galactose-deficient LOS. The LOS may have no α

chain.

[000412] If LOS is present in a vesicle then it is possible to treat the vesicle so as to link its LOS and protein components ("intra-bleb" conjugation (WO04/014417)).

[000413] The immunogenic compositions as disclosed herein may include mixtures of vesicles from different strains. By way of example, WO03/105890 discloses vaccine comprising multivalent meningococcal vesicle compositions, comprising a first vesicle derived from a meningococcal strain with a serosubtype prevalent in a country of use, and a second vesicle derived from a strain that need not have a serosubtype prevent in a country of use. WO06/024946 discloses useful combinations of different vesicles. A combination of vesicles from strains in each of the L2 and L3 immunotypes may be used in some embodiments.

[000414] Vesicle-based antigens can be prepared from *N. meningitidis* serogroups other than serogroup B (*e.g.*, WO01/91788 discloses a process for serogroup A). The immunogenic compositions disclosed herein accordingly can include vesicles prepared serogroups other than B (e.g. A, C, W135 and/or Y) and from bacterial pathogens other than *Neisseria.*

Viral Antigens

[000415] Viral antigens suitable for use in the immunogenic compositions provided herein include, but are not limited to, inactivated (or killed) virus, attenuated virus, split virus formulations, purified subunit formulations, viral proteins which may be isolated, purified or derived from a virus, and Virus Like Particles (VLPs). In certain embodiments, viral antigens are derived from viruses propagated on cell culture or other substrate. In other embodiments, viral antigens are expressed recombinantly. In certain embodiments, viral antigens preferably include epitopes which are exposed on the surface of the virus during at least one stage of its life cycle. Viral antigens are preferably conserved across multiple serotypes or isolates. Viral antigens suitable for use in the immunogenic compositions provided herein include, but are not limited to, antigens derived from one or more of the viruses set forth below as well as the specific antigens examples identified below.

Orthomyxovirus: Viral antigens include, but are not limited to, those derived from an Orthomyxovirus, such as Influenza A, B and C. In certain embodiments, orthomyxovirus antigens are selected from one or more of the viral proteins, including hemagglutinin (HA), neuraminidase (NA), nucleoprotein (NP), matrix protein (M1), membrane protein (M2), one or more of the transcriptase components (PB1, PB2 and

PA). In certain embodiments the viral antigen include HA and NA. In certain embodiments, the influenza antigens are derived from interpandemic (annual) flu strains, while in other embodiments, the influenza antigens are derived from strains with the potential to cause pandemic a pandemic outbreak (i.e., influenza strains with new haemagglutinin compared to the haemagglutinin in currently circulating strains, or influenza strains which are pathogenic in avian subjects and have the potential to be transmitted horizontally in the human population, or influenza strains which are pathogenic to humans).

Paramyxoviridae viruses: Viral antigens include, but are not limited to, those derived from Paramyxoviridae viruses, such as Pneumoviruses (RSV), Paramyxoviruses (PIV), Metapneumovirus and Morbilliviruses (Measles).

Pneumovirus: Viral antigens include, but are not limited to, those derived from a Pneumovirus, such as Respiratory syncytial virus (RSV), Bovine respiratory syncytial virus, Pneumonia virus of mice, and Turkey rhinotracheitis virus. Preferably, the Pneumovirus is RSV. In certain embodiments, pneumovirus antigens are selected from one or more of the following proteins, including surface proteins Fusion (F), Glycoprotein (G) and Small Hydrophobic protein (SH), matrix proteins M and M2, nucleocapsid proteins N, P and L and nonstructural proteins NS1 and NS2. In other embodiments, pneumovirus antigens include F, G and M. In certain embodiments, pneumovirus antigens are also formulated in or derived from chimeric viruses, such as, by way of example only, chimeric RSV/PIV viruses comprising components of both RSV and PIV.

Paramyxovirus: Viral antigens include, but are not limited to, those derived from a Paramyxovirus, such as Parainfluenza virus types 1 – 4 (PIV), Mumps, Sendai viruses, Simian virus 5, Bovine parainfluenza virus, Nipahvirus, Henipavirus and Newcastle disease virus. In certain embodiments, the Paramyxovirus is PIV or Mumps. In certain embodiments, paramyxovirus antigens are selected from one or more of the following proteins: Hemagglutinin –Neuraminidase (HN), Fusion proteins F1 and F2, Nucleoprotein (NP), Phosphoprotein (P), Large protein (L), and Matrix protein (M). In other embodiments, paramyxovirus proteins include HN, F1 and F2. In certain embodiments, paramyxovirus antigens are also formulated in or derived from chimeric viruses, such as, by way of example only, chimeric RSV/PIV viruses

comprising components of both RSV and PIV. Commercially available mumps vaccines include live attenuated mumps virus, in either a monovalent form or in combination with measles and rubella vaccines (MMR). In other embodiments, the Paramyxovirus is Nipahvirus or Henipavirus and the anitgens are selected from one or more of the following proteins: Fusion (F) protein, Glycoprotein (G) protein, Matrix (M) protein, Nucleocapsid (N) protein, Large (L) protein and Phosphoprotein (P).

Poxviridae: Viral antigens include, but are not limited to, those derived from *Orthopoxvirus* such as *Variola vera*, including but not limited to, *Variola major* and *Variola minor.*

Metapneumovirus: Viral antigens include, but are not limited to, Metapneumovirus, such as human metapneumovirus (hMPV) and avian metapneumoviruses (aMPV). In certain embodiments, metapneumovirus antigens are selected from one or more of the following proteins, including surface proteins Fusion (F), Glycoprotein (G) and Small Hydrophobic protein (SH), matrix proteins M and M2, nucleocapsid proteins N, P and L. In other embodiments, metapneumovirus antigens include F, G and M. In certain embodiments, metapneumovirus antigens are also formulated in or derived from chimeric viruses.

Morbillivirus: Viral antigens include, but are not limited to, those derived from a Morbillivirus, such as Measles. In certain embodiments, morbillivirus antigens are selected from one or more of the following proteins: hemagglutinin (H), Glycoprotein (G), Fusion factor (F), Large protein (L), Nucleoprotein (NP), Polymerase phosphoprotein (P), and Matrix (M). Commercially available measles vaccines include live attenuated measles virus, typically in combination with mumps and rubella (MMR).

Picornavirus: Viral antigens include, but are not limited to, those derived from Picornaviruses, such as Enteroviruses, Rhinoviruses, Heparnavirus, Cardioviruses and Aphthoviruses. In certain embodiments, the antigens are derived from Enteroviruses, while in other embodiments the enterovirus is Poliovirus. In still other embodiments, the antigens are derived from Rhinoviruses. In certain embodiments, the antigens are formulated into virus-like particles (VLPs).

Enterovirus: Viral antigens include, but are not limited to, those derived from an Enterovirus, such as Poliovirus types 1, 2 or 3, Coxsackie A virus types 1 to 22 and 24, Coxsackie B virus types 1 to 6, Echovirus (ECHO) virus) types 1 to 9, 11 to 27

and 29 to 34 and Enterovirus 68 to 71. In certain embodiments, the antigens are derived from Enteroviruses, while in other embodiments the enterovirus is Poliovirus. In certain embodiments, the enterovirus antigens are selected from one or more of the following Capsid proteins VP0, VP1, VP2, VP3 and VP4. Commercially available polio vaccines include Inactivated Polio Vaccine (IPV) and Oral poliovirus vaccine (OPV). In certain embodiments, the antigens are formulated into virus-like particles.

Bunyavirus: Viral antigens include, but are not limited to, those derived from an *Orthobunyavirus*, such as California encephalitis virus, a *Phlebovirus*, such as Rift Valley Fever virus, or a *Nairovirus*, such as *Crimean-Congo hemorrhagic fever* virus.

Rhinovirus: Viral antigens include, but are not limted to, those derived from rhinovirus. In certain embodiments, the rhinovirus antigens are selected from one or more of the following Capsid proteins: VP0, VP1, VP2, VP2 and VP4. In certain embodiments, the antigens are formulated into virus-like particles (VLPs).

Heparnavirus: Viral antigens include, but are not limited to, those derived from a Heparnavirus, such as, by way of example only, Hepatitis A virus (HAV). Commercially available HAV vaccines include inactivated HAV vaccine.

Togavirus: Viral antigens include, but are not limited to, those derived from a Togavirus, such as a Rubivirus, an Alphavirus, or an Arterivirus. In certain embodiments, the antigens are derived from Rubivirus, such as by way of example only, Rubella virus. In certain embodiments, the togavirus antigens are selected from E1, E2, E3, C, NSP-1, NSPO-2, NSP-3 or NSP-4. In certain embodiments, the togavirus antigens are selected from E1, E2 or E3. Commercially available Rubella vaccines include a live cold-adapted virus, typically in combination with mumps and measles vaccines (MMR).

Flavivirus: Viral antigens include, but are not limited to, those derived from a Flavivirus, such as Tick-borne encephalitis (TBE) virus, Dengue (types 1, 2, 3 or 4) virus, Yellow Fever virus, Japanese encephalitis virus, Kyasanur Forest Virus, West Nile encephalitis virus, St. Louis encephalitis virus, Russian spring-summer encephalitis virus, Powassan encephalitis virus. In certain embodiments, the flavivirus antigens are selected from PrM, M, C, E, NS-1, NS-2a, NS2b, NS3, NS4a, NS4b, and NS5. In certain embodiments, the flavivirus antigens are selected from PrM, M and E.

Commercially available TBE vaccine includes inactivated virus vaccines. In certain embodiments, the antigens are formulated into virus-like particles (VLPs).

Pestivirus: Viral antigens include, but are not limited to, those derived from a Pestivirus, such as Bovine viral diarrhea (BVDV), Classical swine fever (CSFV) or Border disease (BDV).

Hepadnavirus: Viral antigens include, but are not limited to, those derived from a Hepadnavirus, such as Hepatitis B virus. In certain embodiments, the hepadnavirus antigens are selected from surface antigens (L, M and S), core antigens (HBc, HBe). Commercially available HBV vaccines include subunit vaccines comprising the surface antigen S protein.

Hepatitis C virus: Viral antigens include, but are not limited to, those derived from a Hepatitis C virus (HCV). In certain embodiments, the HCV antigens are selected from one or more of E1, E2, E1/E2, NS345 polyprotein, NS 345-core polyprotein, core, and/or peptides from the nonstructural regions. In certain embodiments, the Hepatitis C virus antigens include one or more of the following: HCV E1 and or E2 proteins, E1/E2 heterodimer complexes, core proteins and non-structural proteins, or fragments of these antigens, wherein the non-structural proteins can optionally be modified to remove enzymatic activity but retain immunogenicity. In certain embodiments, the antigens are formulated into virus-like particles (VLPs).

Rhabdovirus: Viral antigens include, but are not limited to, those derived from a Rhabdovirus, such as a Lyssavirus (Rabies virus) and Vesiculovirus (VSV). Rhabdovirus antigens may be selected from glycoprotein (G), nucleoprotein (N), large protein (L), nonstructural proteins (NS). Commercially available Rabies virus vaccine comprise killed virus grown on human diploid cells or fetal rhesus lung cells.

Caliciviridae; Viral antigens include, but are not limited to, those derived from Calciviridae, such as Norwalk virus, and Norwalk-like Viruses, such as Hawaii Virus and Snow Mountain Virus. In certain embodiments, the antigens are formulated into virus-like particles (VLPs).

Coronavirus: Viral antigens include, but are not limited to, those derived from a Coronavirus, SARS, Human respiratory coronavirus, Avian infectious bronchitis (IBV), Mouse hepatitis virus (MHV), and Porcine transmissible gastroenteritis virus (TGEV). In certain embodiments, the coronavirus antigens are selected from spike (S), envelope

(E), matrix (M), nucleocapsid (N), and Hemagglutinin-esterase glycoprotein (HE). In certain embodiments, the coronavirus antigen is derived from a SARS virus. In certain embodiments, the coronavirus is derived from a SARS viral antigen as described in WO 04/92360.

Retrovirus: Viral antigens include, but are not limited to, those derived from a Retrovirus, such as an Oncovirus, a Lentivirus or a Spumavirus. In certain embodiments, the oncovirus antigens are derived from HTLV-1, HTLV-2 or HTLV-5. In certain embodiments, the lentivirus antigens are derived from HIV-1 or HIV-2. In certain embodiments, the antigens are derived from HIV-1 subtypes (or clades), including, but not limited to, HIV-1 subtypes (or clades) A, B, C, D, F, G, H, J. K, O. In other embodiments, the antigens are derived from HIV-1 circulating recombinant forms (CRFs), including, but not limited to, A/B, A/E, A/G, A/G/I, etc. In certain embodiments, the retrovirus antigens are selected from gag, pol, env, tax, tat, rex, rev, nef, vif, vpu, and vpr. In certain embodiments, the HIV antigens are selected from gag (p24gag and p55gag), env (gp160 and gp41), pol, tat, nef, rev vpu, miniproteins, (preferably p55 gag and gp140v delete). In certain embodiments, the HIV antigens are derived from one or more of the following strains: HIV_{IIIb}, HIV_{SF2}, HIV_{LAV}, HIV_{LAI}, HIV_{MN}, HIV-1_{CM235}, HIV-1_{US4}, HIV-1_{SF162}, HIV-1_{TV1}, HIV-1_{MJ4},. In certain embodiments, the antigens are derived from endogenous human retroviruses, including, but not limited to, HERV-K ("old" HERV-K and "new" HERV-K).

Reovirus: Viral antigens include, but are not limited to, those derived from a Reovirus, such as an Orthoreovirus, a Rotavirus, an Orbivirus, or a Coltivirus. In certain embodiments, the reovirus antigens are selected from structural proteins λ1, λ2, λ3, μ1, μ2, σ1, σ2, or σ3, or nonstructural proteins σNS, μNS, or σ1s. In certain embodiments, the reovirus antigens are derived from a Rotavirus. In certain embodiments, the rotavirus antigens are selected from VP1, VP2, VP3, VP4 (or the cleaved product VP5 and VP8), NSP 1, VP6, NSP3, NSP2, VP7, NSP4, or NSP5. In certain embodiments, the rotavirus antigens include VP4 (or the cleaved product VP5 and VP8), and VP7.

Parvovirus: Viral antigens include, but are not limited to, those derived from a Parvovirus, such as Parvovirus B19. In certain embodiments, the Parvovirus antigens are selected from VP-1, VP-2, VP-3, NS-1 and NS-2. In certain embodiments, the Parvovirus

antigen is capsid protein VP1 or VP-2. In certain embodiments, the antigens are formulated into virus-like particles (VLPs).

Delta hepatitis virus (HDV): Viral antigens include, but are not limited to, those derived from HDV, particularly δ-antigen from HDV.

Hepatitis E virus (HEV): Viral antigens include, but are not limited to, those derived from HEV.

Hepatitis G virus (HGV): Viral antigens include, but are not limited to, those derived from HGV.

Human Herpesvirus: Viral antigens include, but are not limited to, those derived from a Human Herpesvirus, such as, by way of example only, Herpes Simplex Viruses (HSV), Varicella-zoster virus (VZV), Epstein-Barr virus (EBV), Cytomegalovirus (CMV), Human Herpesvirus 6 (HHV6), Human Herpesvirus 7 (HHV7), and Human Herpesvirus 8 (HHV8). In certain embodiments, the Human Herpesvirus antigens are selected from immediate early proteins (α), early proteins (β), and late proteins (γ). In certain embodiments, the HSV antigens are derived from HSV-1 or HSV-2 strains. In certain embodiments, the HSV antigens are selected from glycoproteins gB, gC, gD and gH, fusion protein (gB), or immune escape proteins (gC, gE, or gI). In certain embodiments, the VZV antigens are selected from core, nucleocapsid, tegument, or envelope proteins. A live attenuated VZV vaccine is commercially available. In certain embodiments, the EBV antigens are selected from early antigen (EA) proteins, viral capsid antigen (VCA), and glycoproteins of the membrane antigen (MA). In certain embodiments, the CMV antigens are selected from capsid proteins, envelope glycoproteins (such as gB and gH), and tegument proteins. In other embodiments, CMV antigens may be selected from one or more of the following proteins: pp65, IE1, gB, gD, gH, gL, gM, gN, gO, UL128, UL129, gUL130, UL150, UL131, UL33, UL78, US27, US28, RL5A, RL6, RL10, RL11, RL12, RL13, UL1, UL2, UL4, UL5, UL6, UL7, UL8, UL9, UL10, UL11, UL14, UL15A, UL16, UL17, UL18, UL22A, UL38, UL40, UL41A, UL42, UL116, UL119, UL120, UL121, UL124, UL132, UL147A, UL148, UL142, UL144, UL141, UL140, UL135, UL136, UL138, UL139, UL133, UL135, UL148A, UL148B, UL148C, UL148D, US2, US3, US6, US7, US8, US9, US10, US11, US12, US13, US14, US15, US16, US17, US18, US19, US20, US21, US29, US30 and US34A. CMV antigens may also be fusions of one or more

CMV proteins, such as, by way of example only, pp65/IE1 (Reap *et al.*, *Vaccine* (2007) 25:7441-7449). In certain embodiments, the antigens are formulated into virus-like particles (VLPs).

Papovaviruses: Antigens include, but are not limited to, those derived from Papovaviruses, such as Papillomaviruses and Polyomaviruses. In certain embodiments, the Papillomaviruses include HPV serotypes 1, 2, 4, 5, 6, 8, 11, 13, 16, 18, 31, 33, 35, 39, 41, 42, 47, 51, 57, 58, 63 and 65. In certain embodiments, the HPV antigens are derived from serotypes 6, 11, 16 or 18. In certain embodiments, the HPV antigens are selected from capsid proteins (L1) and (L2), or E1 – E7, or fusions thereof. In certain embodiments, the HPV antigens are formulated into virus-like particles (VLPs). In certain embodiments, the Polyomyavirus viruses include BK virus and JK virus. In certain embodiments, the Polyomavirus antigens are selected from VP1, VP2 or VP3.

Adenovirus: Antigens include those derived from Adenovirus. In certain embodiments, the Adenovirus antigens are derived from Adenovirus serotype 36 (Ad-36). In certain embodiments, the antigen is derived from a protein or peptide sequence encoding an Ad-36 coat protein or fragment thereof (WO 2007/120362).

[000416] Further provided are antigens, compositions, methods, and microbes included in *Vaccines*, 4th Edition (Plotkin and Orenstein ed. 2004); *Medical Microbiology* 4th Edition (Murray et al. ed. 2002); *Virology*, 3rd Edition (W.K. Joklik ed. 1988); *Fundamental Virology*, 2nd Edition (B.N. Fields and D.M. Knipe, eds. 1991), which are contemplated in conjunction with the immunogenic compositions provided herein.

Fungal Antigens

[000417] Fungal antigens for use in the immunogenic compositions provided herein include, but are not limited to, those derived from one or more of the fungi set forth below.

Fungal antigens are derived from Dermatophytres, including: *Epidermophyton floccusum, Microsporum audouini, Microsporum canis, Microsporum distortum, Microsporum equinum, Microsporum gypsum, Microsporum nanum, Trichophyton concentricum, Trichophyton equinum, Trichophyton gallinae, Trichophyton gypseum, Trichophyton megnini, Trichophyton mentagrophytes, Trichophyton quinckeanum, Trichophyton rubrum, Trichophyton schoenleini, Trichophyton tonsurans, Trichophyton verrucosum, T. verrucosum* var. album, var. discoides, var. ochraceum, *Trichophyton violaceum,* and/or *Trichophyton faviforme;* and

Fungal pathogens are derived from *Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger, Aspergillus nidulans, Aspergillus terreus, Aspergillus sydowi, Aspergillus flavatus, Aspergillus glaucus, Blastoschizomyces capitatus, Candida albicans, Candida enolase, Candida tropicalis, Candida glabrata, Candida krusei, Candida parapsilosis, Candida stellatoidea, Candida kusei, Candida parakwsei, Candida lusitaniae, Candida pseudotropicalis, Candida guilliermondi, Cladosporium carrionii, Coccidioides immitis, Blastomyces dermatidis, Cryptococcus neoformans, Geotrichum clavatum, Histoplasma capsulatum, Klebsiella pneumoniae, Microsporidia, Encephalitozoon* spp., *Septata intestinalis* and *Enterocytozoon bieneusi*; the less common are *Brachiola* spp, *Microsporidium* spp., *Nosema* spp., *Pleistophora* spp., *Trachipleistophora* spp., *Vittaforma* spp *Paracoccidioides brasiliensis, Pneumocystis carinii, Pythiumn insidiosum, Pityrosporum ovale, Sacharomyces cerevisae, Saccharomyces boulardii, Saccharomyces pombe, Scedosporium apiosperum, Sporothrix schenckii, Trichosporon beigelii, Toxoplasma gondii, Penicillium marneffei,* Malassezia spp., Fonsecaea spp., Wangiella spp., Sporothrix spp., Basidiobolus spp., Conidiobolus spp., Rhizopus spp, Mucor spp, Absidia spp, Mortierella spp, Cunninghamella spp, Saksenaea spp., Alternaria spp, Curvularia spp, Helminthosporium spp, Fusarium spp, Aspergillus spp, Penicillium spp, Monolinia spp, Rhizoctonia spp, Paecilomyces spp, Pithomyces spp, and Cladosporium spp.

[000418] In certain embodiments, the process for producing a fungal antigen includes a method wherein a solubilized fraction extracted and separated from an insoluble fraction obtainable from fungal cells of which cell wall has been substantially removed or at least partially removed, characterized in that the process comprises the steps of: obtaining living fungal cells; obtaining fungal cells of which cell wall has been substantially removed or at least partially removed; bursting the fungal cells of which cell wall has been substantially removed or at least partially removed; obtaining an insoluble fraction; and extracting and separating a solubilized fraction from the insoluble fraction.

Protazoan Antigens/Pathogens

[000419] Protazoan antigens/pathogens for use in the immunogenic compositions provided herein include, but are not limited to, those derived from one or more of the following protozoa: *Entamoeba histolytica, Giardia lambli,* Cryptosporidium parvum, Cyclospora cayatanensis and

Toxoplasma.

Plant Antigens/Pathogens

Plan antigens/pathogens for use in the immunogenic compositions provided herein include, but are not limited to, those derived from *Ricinus communis.*

STD Antigens

[000420] In certain embodiments, the immunogenic compositions provided herein include one or more antigens derived from a sexually transmitted disease (STD). In certain embodiments, such antigens provide for prophylactis for STD's such as chlamydia, genital herpes, hepatitis (such as HCV), genital warts, gonorrhea, syphilis and/or chancroid. In other embodiments, such antigens provide for therapy for STD's such as chlamydia, genital herpes, hepatitis (such as HCV), genital warts, gonorrhea, syphilis and/or chancroid. Such antigens are derived from one or more viral or bacterial STD's. In certain embodiments, the viral STD antigens are derived from HIV, herpes simplex virus (HSV-1 and HSV-2), human papillomavirus (HPV), and hepatitis (HCV). In certain embodiments, the bacterial STD antigens are derived from *Neiserria gonorrhoeae, Chlamydia trachomatis, Treponema pallidum, Haemophilus ducreyi, E. coli,* and *Streptococcus agalactiae.* Examples of specific antigens derived from these pathogens are described above.

Respiratory Antigens

[000421] In certain embodiments, the immunogenic compositions provided herein include one or more antigens derived from a pathogen which causes respiratory disease. By way of example only, such respiratory antigens are derived from a respiratory virus such as Orthomyxoviruses (influenza), Pneumovirus (RSV), Paramyxovirus (PIV), Morbillivirus (measles), Togavirus (Rubella), VZV, and Coronavirus (SARS). In certain embodiments, the respiratory antigens are derived from a bacteria which causes respiratory disease, such as, by way of example only, *Streptococcus pneumoniae, Pseudomonas aeruginosa, Bordetella pertussis, Mycobacterium tuberculosis, Mycoplasma pneumoniae, Chlamydia pneumoniae, Bacillus anthracis,* and *Moraxella catarrhalis.* Examples of specific antigens derived from these pathogens are described above.

Pediatric Vaccine Antigens

[000422] In certain embodiments, the immunogenic compositions provided herein include one or more antigens suitable for use in pediatric subjects. Pediatric subjects are typically less than about 3 years old, or less than about 2 years old, or less than about 1 years old. Pediatric antigens are administered multiple times over the course of 6 months, 1, 2 or 3 years. Pediatric antigens are

derived from a virus which may target pediatric populations and/or a virus from which pediatric populations are susceptible to infection. Pediatric viral antigens include, but are not limited to, antigens derived from one or more of Orthomyxovirus (influenza), Pneumovirus (RSV), Paramyxovirus (PIV and Mumps), Morbillivirus (measles), Togavirus (Rubella), Enterovirus (polio), HBV, Coronavirus (SARS), and Varicella-zoster virus (VZV), Epstein Barr virus (EBV). Pediatric bacterial antigens include antigens derived from one or more of *Streptococcus pneumoniae*, *Neisseria meningitides*, *Streptococcus pyogenes* (Group A Streptococcus), *Moraxella catarrhalis*, *Bordetella pertussis*, *Staphylococcus aureus*, *Clostridium tetani* (Tetanus), *Cornynebacterium diphtheriae* (Diphtheria), *Haemophilus influenzae B* (Hib), *Pseudomonas aeruginosa*, *Streptococcus agalactiae* (Group B Streptococcus), and *E. coli*. Examples of specific antigens derived from these pathogens are described above.

Antigens suitable for use in Elderly or Immunocompromised Individuals

[000423] In certain embodiments, the immunogenic compositions provided herein include one or more antigens suitable for use in elderly or immunocompromised individuals. Such individuals may need to be vaccinated more frequently, with higher doses or with adjuvanted formulations to improve their immune response to the targeted antigens. Antigens which are targeted for use in Elderly or Immunocompromised individuals include antigens derived from one or more of the following pathogens: Neisseria meningitides, Streptococcus pneumoniae, Streptococcus pyogenes *(Group A Streptococcus)*, Moraxella catarrhalis, Bordetella pertussis, Staphylococcus aureus, Staphylococcus epidermis, Clostridium tetani *(Tetanus)*, Cornynebacterium diphtheriae *(Diphtheria)*, Haemophilus influenzae B *(Hib)*, Pseudomonas aeruginosa, Legionella pneumophila, Streptococcus agalactiae *(Group B Streptococcus)*, Enterococcus faecalis, Helicobacter pylori, Chlamydia pneumoniae, Orthomyxovirus (influenza), Pneumovirus (RSV), Paramyxovirus (PIV and Mumps), Morbillivirus (measles), Togavirus (Rubella), Enterovirus (polio), HBV, Coronavirus (SARS), Varicella-zoster virus (VZV), Epstein Barr virus (EBV), Cytomegalovirus (CMV). Examples of specific antigens derived from these pathogens are described above.

Antigens suitable for use in Adolescent Vaccines

[000424] In certain embodiments, the immunogenic compositions provided herein include one or more antigens suitable for use in adolescent subjects. Adolescents are in need of a boost of a previously administered pediatric antigen. Pediatric antigens which are suitable for use in adolescents are described above. In addition, adolescents are targeted to receive antigens derived

from an STD pathogen in order to ensure protective or therapeutic immunity before the beginning of sexual activity. STD antigens which are suitable for use in adolescents are described above.

Tumor Antigens

[000425] In certain embodiments, a tumor antigen or cancer antigen is used in conjunction with the immunogenic compositions provided herein. In certain embodiments, the tumor antigens is a peptide-containing tumor antigens, such as a polypeptide tumor antigen or glycoprotein tumor antigens. In certain embodiments, the tumor antigen is a saccharide-containing tumor antigen, such as a glycolipid tumor antigen or a ganglioside tumor antigen. In certain embodiments, the tumor antigen is a polynucleotide-containing tumor antigen that expresses a polypeptide-containing tumor antigen, for instance, an RNA vector construct or a DNA vector construct, such as plasmid DNA.

[000426] Tumor antigens appropriate for the use in conjunction with the immunogenic compositions provided herein encompass a wide variety of molecules, such as (a) polypeptide-containing tumor antigens, including polypeptides (which can range, for example, from 8-20 amino acids in length, although lengths outside this range are also common), lipopolypeptides and glycoproteins, (b) saccharide-containing tumor antigens, including poly-saccharides, mucins, gangliosides, glycolipids and glycoproteins, and (c) polynucleotides that express antigenic polypeptides.

[000427] In certain embodiments, the tumor antigens are, for example, (a) full length molecules associated with cancer cells, (b) homologs and modified forms of the same, including molecules with deleted, added and/or substituted portions, and (c) fragments of the same. In certain embodiments, the tumor antigens are provided in recombinant form. In certain embodiments, the tumor antigens include, for example, class I-restricted antigens recognized by CD8+ lymphocytes or class II-restricted antigens recognized by CD4+ lymphocytes.

[000428] In certain embodiments, the tumor antigens include, but are not limited to, (a) cancer-testis antigens such as NY-ESO-1, SSX2, SCP1 as well as RAGE, BAGE, GAGE and MAGE family polypeptides, for example, GAGE-1, GAGE-2, MAGE-1, MAGE-2, MAGE-3, MAGE-4, MAGE-5, MAGE-6, and MAGE-12 (which can be used, for example, to address melanoma, lung, head and neck, NSCLC, breast, gastrointestinal, and bladder tumors), (b) mutated antigens, for example, p53 (associated with various solid tumors, e.g., colorectal, lung, head and neck cancer), p21/Ras (associated with, e.g., melanoma, pancreatic cancer and colorectal cancer), CDK4 (associated with, e.g., melanoma), MUM1 (associated with, e.g., melanoma), caspase-8 (associated

with, e.g., head and neck cancer), CIA 0205 (associated with, e.g., bladder cancer), HLA-A2-R1701, beta catenin (associated with, e.g., melanoma), TCR (associated with, e.g., T-cell non-Hodgkins lymphoma), BCR-abl (associated with, e.g., chronic myelogenous leukemia), triosephosphate isomerase, KIA 0205, CDC-27, and LDLR-FUT, (c) over-expressed antigens, for example, Galectin 4 (associated with, e.g., colorectal cancer), Galectin 9 (associated with, e.g., Hodgkin's disease), proteinase 3 (associated with, e.g., chronic myelogenous leukemia), WT 1 (associated with, e.g., various leukemias), carbonic anhydrase (associated with, e.g., renal cancer), aldolase A (associated with, e.g., lung cancer), PRAME (associated with, e.g., melanoma), HER-2/neu (associated with, e.g., breast, colon, lung and ovarian cancer), alpha-fetoprotein (associated with, e.g., hepatoma), KSA (associated with, e.g., colorectal cancer), gastrin (associated with, e.g., pancreatic and gastric cancer), telomerase catalytic protein, MUC-1 (associated with, e.g., breast and ovarian cancer), G-250 (associated with, e.g., renal cell carcinoma), p53 (associated with, e.g., breast, colon cancer), and carcinoembryonic antigen (associated with, e.g., breast cancer, lung cancer, and cancers of the gastrointestinal tract such as colorectal cancer), (d) shared antigens, for example, melanoma-melanocyte differentiation antigens such as MART-1/Melan A, gp100, MC1R, melanocyte-stimulating hormone receptor, tyrosinase, tyrosinase related protein-1/TRP1 and tyrosinase related protein-2/TRP2 (associated with, e.g., melanoma), (e) prostate associated antigens such as PAP, PSA, PSMA, PSH-P1, PSM-P1, PSM-P2, associated with e.g., prostate cancer, (f) immunoglobulin idiotypes (associated with myeloma and B cell lymphomas, for example), and (g) other tumor antigens, such as polypeptide- and saccharide-containing antigens including (i) glycoproteins such as sialyl Tn and sialyl Le^x (associated with, e.g., breast and colorectal cancer) as well as various mucins; glycoproteins are coupled to a carrier protein (e.g., MUC-1 are coupled to KLH); (ii) lipopolypeptides (e.g., MUC-1 linked to a lipid moiety); (iii) polysaccharides (e.g., Globo H synthetic hexasaccharide), which are coupled to a carrier proteins (e.g., to KLH), (iv) gangliosides such as GM2, GM12, GD2, GD3 (associated with, e.g., brain, lung cancer, melanoma), which also are coupled to carrier proteins (e.g., KLH).

[000429] In certain embodiments, the tumor antigens include, but are not limited to, p15, Hom/Mel-40, H-Ras, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, Epstein Barr virus antigens, EBNA, human papillomavirus (HPV) antigens, including E6 and E7, hepatitis B and C virus antigens, human T-cell lymphotropic virus antigens, TSP-180, p185erbB2, p180erbB-3, c-met, mn-23H1, TAG-72-4, CA 19-9, CA 72-4, CAM 17.1, NuMa, K-ras, p16, TAGE, PSCA, CT7, 43-9F, 5T4, 791 Tgp72, beta-HCG, BCA225, BTAA, CA 125, CA 15-3 (CA 27.29\BCAA), CA 195,

CA 242, CA-50, CAM43, CD68\KP1, CO-029, FGF-5, Ga733 (EpCAM), HTgp-175, M344, MA-50, MG7-Ag, MOV18, NB/70K, NY-CO-1, RCAS1, SDCCAG16, TA-90 (Mac-2 binding protein\cyclophilin C-associated protein), TAAL6, TAG72, TLP, TPS, and the like.

[000430] Polynucleotide-containing antigens used in conjunction with the immunogenic compositions provided herein include polynucleotides that encode polypeptide cancer antigens such as those listed above. In certain embodiments, the polynucleotide-containing antigens include, but are not limited to, DNA or RNA vector constructs, such as plasmid vectors (e.g., pCMV), which are capable of expressing polypeptide cancer antigens *in vivo*.

[000431] In certain embodiments, the tumor antigens are derived from mutated or altered cellular components. After alteration, the cellular components no longer perform their regulatory functions, and hence the cell may experience uncontrolled growth. Representative examples of altered cellular components include, but are not limited to ras, p53, Rb, altered protein encoded by the Wilms' tumor gene, ubiquitin, mucin, protein encoded by the DCC, APC, and MCC genes, as well as receptors or receptor-like structures such as neu, thyroid hormone receptor, platelet derived growth factor (PDGF) receptor, insulin receptor, epidermal growth factor (EGF) receptor, and the colony stimulating factor (CSF) receptor.

[000432] Additionally, bacterial and viral antigens, are used in conjunction with the immunogenic compositions provided herein for the treatment of cancer. In certain embodiments, the, carrier proteins, such as CRM_{197}, tetanus toxoid, or *Salmonella typhimurium* antigen are used in conjunction/conjugation with compounds provided herein for treatment of cancer. The cancer antigen combination therapies will show increased efficacy and bioavailability as compared with existing therapies.

[000433] In certain embodiments, the immunogenic compositions containing at least one compound of Formula (I) include capsular saccharides from at least two of serogroups A, C, W135 and Y of Neisseria meningitides. In other embodiments, such vaccines further comprise an antigen from one or more of the following: (a) serogroup B N. meningitidis; (b) Haemophilus influenzae type B; and/or (c) Streptococcus pneumoniae.

[000434] In certain embodiments the immunogenic compositions containing at least one compound of Formula (I) include serogroups C, W135 & Y of N. meningitides. In certain embodiments the immunogenic compositions containing at least one compound of Formula (I) include serogroups A, C, W135 & Y of N. meningitides. In certain embodiments the immunogenic compositions containing at least one compound of Formula (I) include serogroups B, C, W135 &

Y of N. meningitides. In certain embodiments the immunogenic compositions containing at least one compound of Formula (I) include serogroups A, B, C, W135 & Y of N. meningitides. In certain embodiments the immunogenic compositions containing at least one compound of Formula (I) include H. influenzae type B and serogroups C, W135 & Y of N. meningitides. In certain embodiments the immunogenic compositions containing at least one compound of Formula (I) include H. influenzae type B and serogroups A, C, W135 & Y of N. meningitides. In certain embodiments the immunogenic compositions containing at least one compound of Formula (I) include H. influenzae type B and serogroups B, C, W135 & Y of N. meningitides. In certain embodiments the immunogenic compositions containing at least one compound of Formula (I) include H. influenzae type B and serogroups A, B, C, W135 & Y of N. meningitides. In certain embodiments the immunogenic compositions containing at least one compound of Formula (I) include S. pneumoniae and serogroups C, W135 & Y of N. meningitides. In certain embodiments the immunogenic compositions containing at least one compound of Formula (I) include S. pneumoniae and serogroups A, C, W135 & Y of N. meningitides. In certain embodiments the immunogenic compositions containing at least one compound of Formula (I) include S. pneumoniae and serogroups B, C, W135 & Y of N. meningitides. In certain embodiments the immunogenic compositions containing at least one compound of Formula (I) include S. pneumoniae and serogroups A, B, C, W135 & Y of N. meningitides. In certain embodiments the immunogenic compositions containing at least one compound of Formula (I) include H. influenzae type B, S. pneumoniae and serogroups C, W135 & Y of N. meningitides. In certain embodiments the immunogenic compositions containing at least one compound of Formula (I) include H. influenzae type B, S. pneumoniae and serogroups A, C, W135 & Y of N. meningitides. In certain embodiments the immunogenic compositions containing at least one compound of Formula (I) include H. influenzae type B, S. pneumoniae and serogroups B, C, W135 & Y of N. meningitides. In certain embodiments the immunogenic compositions containing at least one compound of Formula (I) include H. influenzae type B, S. pneumoniae and serogroups A, B, C, W135 & Y of N. meningitidis.

Kits

[000435] Also provided herein are pharmaceutical packs or kits that include one or more containers containing a compound of Formula (I)-(XVI) useful for the treatment or prevention of a disease or disorder associated with toll-like receptors. In other embodiments, the such pharmaceutical packs or kits include one or more containers containing a compound of Formula

(I)-(XVI) useful for the treatment or prevention of a disease or disorder associated with toll-like receptors and one or more containers containing an additional therapeutic agent, including but not limited to those listed above. In certain embodiments, such pharmaceutical packs or kits optionally include instructions for its administration of a compound of Formula (I)-(XVI) as disclosed herein. In some embodiments of such kits, the compound of Formula (I)-(XVI) is provided in the form of a vaccine composition as described herein, and optionally includes a syringe for injecting a subject with the vaccine composition

Methods of treatment, prevention and administration of vaccines

[000436] The immunogenic compositions as disclosed herein may be used in conjuction with vaccines to improve the immunogenicity of the vaccine or where the immunogenic composition includes one or more antigens, the immunogenic composition may be used as a vaccine. Therefore in certain embodiment, the immunogenic compositions disclosed herein may be used in a method for raising or enhancing an immune response in a mammal comprising the step of administering an effective amount of an immunogenic composition as disclosed herein. The immune response is preferably protective and preferably involves antibodies and/or cell-mediated immunity. The method may raise a booster response.

[000437] In certain embodimentsembodiments, the immunogenic compositions disclosed herein may be used as a medicament, *e.g.*, for use in raising or enhancing an immune response in a mammal.

[000438] In certain embodiments, the immunogenic compositions disclosed herein may be used in the manufacture of a medicament for raising an immune response in a mammal.

[000439] The invention also provides a delivery device pre-filled with an immunogenic composition disclosed herein.

[000440] By raising an immune response in the mammal by these uses and methods, the mammal can be infection by pathogens comprising the antigen included in the immunogenic composition or administered in conjunction with the immunogenic composition can be reduced or even prevented. The mammal is preferably a human, but may be, *e.g.*, a cow, a pig, a chicken, a cat or a dog, as the pathogens covered herein may be problematic across a wide range of species. Where the vaccine is for prophylactic use, the human is preferably a child (*e.g.*, a toddler or infant) or a teenager; where the vaccine is for therapeutic use, the human is preferably a teenager or an adult. A vaccine intended for children may also be administered to adults, *e.g.*, to assess safety, dosage,

immunogenicity, etc.

[000441] One way of checking efficacy of therapeutic treatment involves monitoring pathogen infection after administration of the immunogenic compositions disclosed herein. One way of checking efficacy of prophylactic treatment involves monitoring immune responses, systemically (such as monitoring the level of IgG1 and IgG2a production) and/or mucosally (such as monitoring the level of IgA production), against the antigens included in or administered in conjunction with the immunogenic compositions disclosed herein after administration of the immunogenic composition (and the antigen if administered separately). Typically, antigen-specific serum antibody responses are determined post-immunisation but pre-challenge whereas antigen-specific mucosal antibody responses are determined post-immunisation and post-challenge.

[000442] Another way of assessing the immunogenicity of the immunogenic compositions disclosed herein where the antigen is a protein is to express the proteins recombinantly for screening patient sera or mucosal secretions by immunoblot and/or microarrays. A positive reaction between the protein and the patient sample indicates that the patient has mounted an immune response to the protein in question. This method may also be used to identify immunodominant antigens and/or epitopes within protein antigens.

[000443] The efficacy of the immunogenic compositions can also be determined *in vivo* by challenging appropriate animal models of the pathogen of interest infection.

[000444] The immunogenic compositions disclosed herein will generally be administered directly to a subject. Direct delivery may be accomplished by parenteral injection (*e.g.*, subcutaneously, intraperitoneally, intravenously, intramuscularly, or to the interstitial space of a tissue), or mucosally, such as by rectal, oral (*e.g.*, tablet, spray), vaginal, topical, transdermal or transcutaneous, intranasal, ocular, aural, pulmonary or other mucosal administration.

[000445] The immunogenic compositions may be used to elicit systemic and/or mucosal immunity, preferably to elicit an enhanced systemic and/or mucosal immunity.

[000446] Preferably the enhanced systemic and/or mucosal immunity is reflected in an enhanced TH1 and/or TH2 immune response. Preferably, the enhanced immune response includes an increase in the production of IgG1 and/or IgG2a and/or IgA.

[000447] Dosage can be by a single dose schedule or a multiple dose schedule. Multiple doses may be used in a primary immunisation schedule and/or in a booster immunisation schedule. In a

multiple dose schedule the various doses may be given by the same or different routes, *e.g.*, a parenteral prime and mucosal boost, a mucosal prime and parenteral boost, etc. Multiple doses will typically be administered at least 1 week apart (*e.g.*, about 2 weeks, about 3 weeks, about 4 weeks, about 6 weeks, about 8 weeks, about 10 weeks, about 12 weeks, about 16 weeks, etc.).

[000448] The immunogenic compositions disclosed herein that include one or more antigens or are used in conjunction with one or more antigens may be used to treat both children and adults. Thus a human subject may be less than 1 year old, 1-5 years old, 5-15 years old, 15-55 years old, or at least 55 years old. Preferred subjects for receiving such immunogenic compositions are the elderly (*e.g.*, >50 years old, >60 years old, and preferably >65 years), the young (*e.g.*, <5 years old), hospitalised patients, healthcare workers, armed service and military personnel, pregnant women, the chronically ill, or immunodeficient patients. The immunogenic compositions are not suitable solely for these groups, however, and may be used more generally in a population.

[000449] The immunogenic compositions disclosed herein that include one or more antigens or are used in conjunction with one or more antigens may be administered to patients at substantially the same time as (*e.g.*, during the same medical consultation or visit to a healthcare professional or vaccination centre) other vaccines, *e.g.*, at substantially the same time as a measles vaccine, a mumps vaccine, a rubella vaccine, a MMR vaccine, a varicella vaccine, a MMRV vaccine, a diphtheria vaccine, a tetanus vaccine, a pertussis vaccine, a DTP vaccine, a conjugated *H. influenzae* type b vaccine, an inactivated poliovirus vaccine, a hepatitis B virus vaccine, a meningococcal conjugate vaccine (such as a tetravalent A C W135 Y vaccine), a respiratory syncytial virus vaccine, etc.

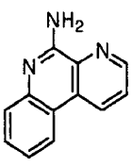
Examples

[000450] The following examples were offered to illustrate, but not to limit, the compounds of Formula (I) provided herein, and the preparation of such compounds.

Preparation of Benzo[f][1,7]naphthyridin-5-amine analogs

Example 1

Benzo[f][1,7]naphthyridin-5-amine

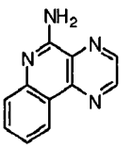


[000451] A solution of 2-(*tert*-butoxycarbonylamino)phenylboronic acid (1.0 eq.) and 3-

bromopicolino-nitrile (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give a white solid. ^1H NMR (acetone *d*-6): δ 9.04 (d, 1H), 8.91 (d, 1H), 8.45 (d, 1H), 7.86 (dd, 1H), 7.53-7.62 (m, 2H), 7.35 (t, 1H), 6.65 (br, 2H). LRMS [M+H] = 196.1

Example 2

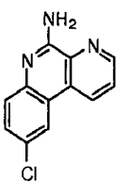
Pyrazino[2,3-c]quinolin-5-amine



[000452] A solution of 2-(*tert*-butoxycarbonylamino)phenylboronic acid (1.0 eq.) and 3-chloropyrazine-2-carbonitrile (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-50% ethyl acetate in hexane to give a solid. ^1H NMR (acetone *d*-6): δ 9.14 (s, 1H), 8.95 (s, 1H), 8.77 (d, 1H), 7.63-7.66 (m, 2H), 7.38 (t, 1H), 6.77 (br, 2H). LRMS [M+H] = 197.1

Example 3

9-chlorobenzo[f][1,7]naphthyridin-5-amine



Step 1: tert-butyl 2-bromo-4-chlorophenylcarbamate

[000453] To a solution of 2-bromo-4-chloroaniline (1.0 eq.) in tetrahydrofuran (0.2 M) at 0°C under N_2 atmosphere was added dropwise 1M NaHMDS (2.5 eq.). The reaction was stirred for 15 minutes at 0°C, and a solution of di-*tert*-butyl dicarbonate in tetrahydrofuran was added. The reaction was warmed to room temperature overnight. The solvent was evaporated, and the resulting residue was quenched with 0.1N HCl aqueous solution. The aqueous suspension was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified y by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% ethyl acetate in hexane to give the product as light yellow oil.

Step 2: tert-butyl 4-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl-carbamate

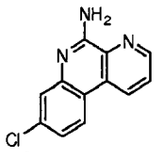
[000454] *Tert*-butyl 2-bromo-4-chlorophenylcarbamate (from step 1) (1.0 eq.), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.5 eq.), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) (5%), and sodium acetate (4.5 eq.) were mixed in dioxane (0.2 M) under N_2 atmosphere. The reaction was heated to 100°C and stirred overnight. The resulting suspension was cooled to ambient temperature, diluted with ether, filtered through celite, and the filtrate was concentrated *en vacuo*. The crude mixture was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-10% ethyl acetate in hexane to give *tert*-butyl 4-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl-carbamate.

Step 3: 9-chlorobenzo[f][1,7]naphthyridin-5-amine

[000455] A solution of *tert*-butyl 4-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl-carbamate (from step 2) (1.0 eq.) and 3-bromopicolino-nitrile (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-50% ethyl acetate in hexane and then re-purified using 0-5% methanol in dichloromethane to give a solid. ^1H NMR (acetone *d*-6): δ 9.08 (d, 1H), 8.96 (d, 1H), 8.45 (s, 1H), 7.86-7.89 (dd, 1H), 7.60 (d, 1H), 7.54 (d, 1H), 6.78 (br, 2H). LRMS [M+H] = 230.1

Example 4

8-chlorobenzo[f][1,7]naphthyridin-5-amine



Step 1: tert-butyl 2-bromo-5-chlorophenylcarbamate

[000456] To a solution of 2-bromo-5-chloroaniline (1.0 eq.) in tetrahydrofuran (0.2 M) at 0°C under N_2 atmosphere was added dropwise 1M NaHMDS (2.5 eq.). The reaction was stirred for 15 minutes at 0°C, and a solution of di-*tert*-butyl dicarbonate in tetrahydrofuran was added. The reaction was warmed to room temperature overnight. The solvent was evaporated, and the resulting residue was quenched with 0.1N HCl aqueous solution. The aqueous suspension was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% ethyl acetate in hexane to give the product as light yellow oil.

Step 2: tert-butyl 5-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl-carbamate

[000457] *Tert*-butyl 2-bromo-5-chlorophenylcarbamate (from step 1) (1.0 eq.), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.5 eq.), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) (5%), and sodium acetate (4.5 eq.) were mixed in dioxane (0.2 M) under N_2 atmosphere. The reaction was heated to 100°C and stirred overnight. The resulting suspension was cooled to ambient temperature, diluted with ether, filtered through celite, and the filtrate was concentrated *en vacuo*. The crude mixture was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% ethyl acetate in hexane to give *tert*-butyl 5-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl-carbamate.

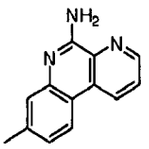
Step 3: 8-chlorobenzo[f][1,7]naphthyridin-5-amine

[000458] A solution of *tert*-butyl 5-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl-carbamate (from step 2) (1.0 eq.) and 3-bromopicolino-nitrile (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified

by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% methanol in dichloromethane to give a semipure solid, which was then stirred in hot 10% ethyl acetate in hexane, filtered, and dried to give a pure solid. ^{1}H NMR (acetone *d*-6): δ 9.03 (d, 1H), 8.93 (d, 1H), 8.46 (d, 1H), 7.85-7.88 (dd, 1H), 7.57 (s, 1H), 7.32 (d, 1H), 6.94 (br, 2H). LRMS [M+H] = 230.1

Example 5

8-methylbenzo[f][1,7]naphthyridin-5-amine



Step 1: tert-butyl 2-bromo-5-methylphenylcarbamate

[000459] To a solution of 2-bromo-5-methylaniline (1.0 eq.) in tetrahydrofuran (0.2 M) at 0°C under N_2 atmosphere was added dropwise 1M NaHMDS (2.5 eq.). The reaction was stirred for 15 minutes at 0°C, and a solution of di-*tert*-butyl dicarbonate in tetrahydrofuran was added. The reaction was warmed to room temperature overnight. The solvent was evaporated, and the resulting residue was quenched with 0.1N HCl aqueous solution. The aqueous suspension was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% ethyl acetate in hexane to give product as light yellow oil.

Step 2: tert-butyl 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate

[000460] *Tert*-butyl 2-bromo-5-methylphenylcarbamate (from step 1) (1.0 eq.), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.5 eq.), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) (5%), and sodium acetate (4.5 eq.) were mixed in dioxane (0.2 M) under N_2 atmosphere. The reaction was heated to 100°C and stirred overnight. The resulting suspension was cooled to ambient temperature, diluted with ether, filtered through celite, and the filtrate was concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-8% ether in hexane to give *tert*-butyl 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate.

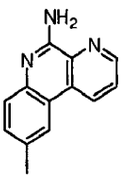
Step 3: 8-methylbenzo[f][1,7]naphthyridin-5-amine

[000461] A solution of *tert*-butyl 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from step 2) (1.0 eq.) and 3-bromopicolino-nitrile (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium

carbonate solution (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-40% ethyl acetate in toluene to give a pure solid. ^1H NMR (acetone *d*-6): δ 8.98 (d, 1H), 8.87 (d, 1H), 8.32 (d, 1H), 7.79-7.82 (dd, 1H), 7.42 (s, 1H), 7.18 (d, 1H), 6.6 (br, 2H), 2.45 (s, 3H). LRMS [M+H] = 210.1

Example 6

9-methylbenzo[f][1,7]naphthyridin-5-amine



Step 1: tert-butyl 2-bromo-4-methylphenylcarbamate

[000462] To a solution of 2-bromo-4-methylaniline (1.0 eq.) in tetrahydrofuran (0.2 M) at 0°C under N_2 atmosphere was added dropwise 1M NaHMDS (2.5 eq.). The reaction was stirred for 15 minutes at 0°C, and a solution of di-*tert*-butyl dicarbonate in tetrahydrofuran was added. The reaction was warmed to room temperature overnight. The solvent was evaporated, and the resulting residue was quenched with 0.1N HCl aqueous solution. The aqueous suspension was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% ethyl acetate in hexane to give product as light yellow oil.

Step 2: tert-butyl 4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate

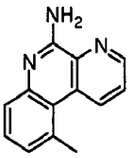
[000463] *Tert*-butyl 2-bromo-4-methylphenylcarbamate (from step 1) (1.0 eq.), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.5 eq.), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) (5%), and sodium acetate (4.5 eq.) were mixed in dioxane (0.2 M) under N_2 atmosphere. The reaction was heated to 100°C and stirred overnight. The resulting suspension was cooled to ambient temperature, diluted with ether, filtered through celite, and the filtrate was concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-8% ether in hexane to give *tert*-butyl 4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate.

Step 3: 9-methylbenzo[f][1,7]naphthyridin-5-amine

[000464] A solution of *tert*-butyl 4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from step 2) (1.0 eq.) and 3-bromopicolino-nitrile (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% methanol in dichloromethane to give a semipure solid, which was then swirled in hot ethyl acetate, filtered, and dried to give a pure solid. ^{1}H NMR (acetone *d*-6): δ 9.02 (d, 1H), 8.89 (d, 1H), 8.25 (s, 1H), 7.80-7.84 (dd, 1H), 7.52 (d, 1H), 7.40 (d, 1H), 6.5 (br, 2H), 2.48 (s, 3H). LRMS [M+H] = 210.2

Example 7

10-methylbenzo[f][1,7]naphthyridin-5-amine



Step 1: tert-butyl 2-bromo-3-methylphenylcarbamate

[000465] To a solution of 2-bromo-3-methylaniline (1.0 eq.) in tetrahydrofuran (0.2 M) at 0°C under N_2 atmosphere was added dropwise 1M NaHMDS (2.5 eq.). The reaction was stirred for 15 minutes at 0°C, and a solution of di-*tert*-butyl dicarbonate in tetrahydrofuran was added. The reaction was warmed to room temperature overnight. The solvent was evaporated, and the resulting residue was quenched with 0.1N HCl aqueous solution. The aqueous suspension was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% ethyl acetate in hexane to give product as light yellow oil.

Step 2: tert-butyl 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate

[000466] *Tert*-butyl 2-bromo-3-methylphenylcarbamate (from step 1) (1.0 eq.), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.5 eq.), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) (5%), and sodium acetate (4.5 eq.) were mixed in dioxane (0.2 M) under N_2 atmosphere. The reaction was heated to 100°C and stirred overnight. The resulting suspension was cooled to ambient temperature, diluted with ether, filtered through

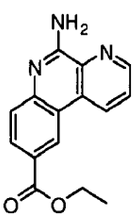
celite, and the filtrate was concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-10% ether in hexane to *tert*-butyl 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate.

Step 3: 10-methylbenzo[f][1,7]naphthyridin-5-amine

[000467] A solution of *tert*-butyl 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from step 2) (1.0 eq.) and 3-bromopicolino-nitrile (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-40% ethyl acetate in toluene to give a semipure solid, which was then swirled in hot 10% ethyl acetate in hexane, filtered, and dried to give a pure solid. ^1H NMR (acetone *d*-6): δ 9.22 (d, 1H), 8.90 (d, 1H), 7.82-7.85 (dd, 1H), 7.54 (d, 1H), 7.45 (t, 1H), 7.19 (d, 1H), 6.6 (br, 2H), 2.98 (s, 3H). LRMS [M+H] = 210.2.

Example 8

Ethyl 5-aminobenzo[f][1,7]naphthyridine-9-carboxylate



Step 1: ethyl 3-bromo-4-(tert-butoxycarbonylamino)benzoate

[000468] To a solution of 4-amino-3-bromobenzoate (1.0 eq.) in tetrahydrofuran (0.2 M) at 0°C under N_2 atmosphere was added dropwise 1M NaHMDS (2.5 eq.). The reaction was stirred for 15 minutes at 0°C, and a solution of di-*tert*-butyl dicarbonate in tetrahydrofuran was added. The reaction was warmed to room temperature overnight. The solvent was evaporated, and the resulting residue was quenched with 0.1N HCl aqueous solution. The aqueous suspension was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% ethyl acetate in hexane to give

product as light yellow oil.

Step 2: Ethyl 4-(tert-butoxycarbonylamino)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

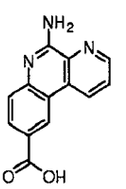
[000469] Ethyl 3-bromo-4-(*tert*-butoxycarbonylamino)benzoate (from step 1) (1.0 eq.), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.5 eq.), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) (5%), and sodium acetate (4.5 eq.) were mixed in dioxane (0.2 M) under N_2 atmosphere. The reaction was heated to 100°C and stirred overnight. The resulting suspension was cooled to ambient temperature, diluted with ether, filtered through celite, and the filtrate was concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-10% ether in hexane to give ethyl 4-(*tert*-butoxycarbonylamino)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate.

Step 3: ethyl 5-aminobenzo[f][1,7]naphthyridine-9-carboxylate

[000470] A solution of ethyl 4-(*tert*-butoxycarbonylamino)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (from step 2) (1.0 eq.) and 3-bromopicolino-nitrile (1.0 eq.) in toluene/ethanol (10:1, 0.23 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and anhydrous potassium carbonate (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-40% ethyl acetate in toluene to give a semipure solid, which was then swirled in hot 10% ethyl acetate in hexane, filtered, and dried to give a pure solid. ^{1}H NMR (acetone *d*-6): δ 9.11 (d, 1H), 9.05 (s, 1H), 8.95 (d, 1H), 8.14 (d, 1H), 7.89-7.92 (dd, 1H), 7.63 (d, 1H), 4.38 (q, 2H), 1.40 (t, 3H). LRMS [M+H] = 268.2.

Example 9

5-aminobenzo[f][1,7]naphthyridine-9-carboxylic acid

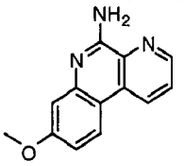


[000471] Ethyl 5-aminobenzo[f][1,7]naphthyridine-9-carboxylate (Example 8) (1.0 eq.) was mixed with 1N NaOH (2.0 eq.) in ethanol (0.12 M). The reaction was heated to 80°C and stirred for 36 hours. The solvent was removed *en vacuo*. The residue was suspended in water, and the pH was adjusted to neutral using 5% citric acid aqueous solution. The suspension was centrifuged

(2500 rpm, 5 min), and the supernatant was removed. The resulting solids was re-suspended in water by vortexing, centrifuged (2500 rpm, 5 min), and the supernatant was removed. The re-suspension, centrifugation, and removal of supernatant steps were repeated with hot methanol, hot ethyl acetate, and ether to give a pure solid. ^{1}H NMR (DMSO): δ 12.86 (s, 1H), 9.15 (d, 1H), 9.00 (s, 1H), 8.97 (d, 1H), 8.07 (d, 1H), 7.88-7.91 (dd, 1H), 7.56-7.59 (m, 3H). LRMS [M+H] = 240.1

Example 10

8-methoxybenzo[f][1,7]naphthyridin-5-amine



Step 1: 2-bromo-5-methoxyaniline

[000472] A solution of 1-bromo-4-methoxy-2-nitrobenzene (1.0 eq.), iron powder (3.0 eq.), and concentrated HCl (1.04 eq.) were mixed together in ethanol (0.64 M) and heated to reflux. The reaction was stirred for 24 hours, and the solvent was evaporated. The resulting residue was diluted with ethyl acetate and saturated aqueous ammonium chloride solution. The aqueous layer was extracted three times with ethyl acetate, and the combined organic layers were washed with water, brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-15% ethyl acetate in hexane to give the product as oil.

Step 2: tert-butyl 2-bromo-5-methoxyphenylcarbamate

[000473] To a solution of 2-bromo-5-methoxyaniline (1.0 eq.) (from step 1) in tetrahydrofuran (0.2 M) at 0°C under N_2 atmosphere was added dropwise 1M NaHMDS (2.5 eq.). The reaction was stirred for 15 minutes at 0°C, and a solution of di-*tert*-butyl dicarbonate in tetrahydrofuran was added. The reaction was warmed to room temperature overnight. The solvent was evaporated, and the resulting residue was quenched with 0.1N HCl aqueous solution. The aqueous suspension was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% ethyl acetate in hexane to give product as light yellow oil.

Step 3: tert-butyl 5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate

[000474] *Tert*-butyl 2-bromo-5-methoxyphenylcarbamate (from step 2) (1.0 eq.), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.5 eq.), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) (5%), and sodium acetate (4.5 eq.) were mixed in

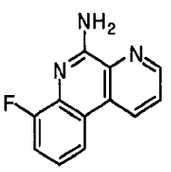
dioxane (0.2 M) under N_2 atmosphere. The reaction was heated to 100°C and stirred overnight. The resulting suspension was cooled to ambient temperature, diluted with ether, filtered through celite, and the filtrate was concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-15% ether in hexane to give *tert*-butyl 5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate.

Step 4: 8-methoxybenzo[f][1,7]naphthyridin-5-amine

[000475] A solution of *tert*-butyl 5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from step 3) (1.0 eq.) and 3-bromopicolino-nitrile (1.0 eq.) in toluene/ethanol (10:1, 0.23 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and anhydrous potassium carbonate (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% methanol in dichloromethane to give a semipure solid, which was then recrystalized in ethyl acetate, filtered, and dried to give a pure solid. ^{1}H NMR (acetone *d*-6): δ 8.91 (d, 1H), 8.82 (d, 1H), 8.33 (d, 1H), 7.76-7.79 (dd, 1H), 7.07 (s, 1H), 6.96 (d, 1H), 6.6 (br, 2H), 3.90 (s, 3H). LRMS [M+H] = 226.1

Example 11

7-fluorobenzo[f][1,7]naphthyridin-5-amine



Step 1: tert-butyl 2-fluorophenylcarbamate

[000476] To a solution of 2-fluoroaniline (1.0 eq.) in tetrahydrofuran (0.2 M) at 0°C under N_2 atmosphere was added dropwise 1M NaHMDS (2.5 eq.). The reaction was stirred for 15 minutes at 0°C, and a solution of di-*tert*-butyl dicarbonate in tetrahydrofuran was added. The reaction was warmed to room temperature overnight. The solvent was evaporated, and the resulting residue was quenched with 0.1N HCl aqueous solution. The aqueous suspension was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% ethyl acetate in hexane to give product as light

yellow oil.

Step 2: 2-(tert-butoxycarbonylamino)-3-fluorophenylboronic acid

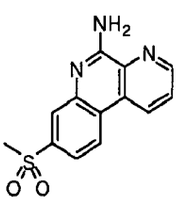
[000477] To a solution of *tert*-butyl 2-fluorophenylcarbamate (from step 1) (1.0 eq.) in tetrahydrofuran (0.25 M) at -78°C under N_2 atmosphere was added dropwise 1.7 M *tert*-butyllithium (2.4 eq.). The reaction was warmed to -40°C slowly over 2 hours, and neat trimethyl borate (3.8 eq.) was added. The reaction was warmed to room temperature over 30 minutes. An aqueous solution of 1N NaOH was slowly added to the reaction and stirred for 15 minutes. The mixture was poured into ethyl acetate and acidified with 3N HCl to dissolve the solids. The aqueous layer was extracted twice with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The resulting solids were stirred in 1:1 ether/hexane, filtered, and dried. The solids were carried onto the next step without further purification.

Step 3: 7-fluorobenzo[f][1,7]naphthyridin-5-amine

[000478] A solution of 2-(tert-butoxycarbonylamino)-3-fluorophenylboronic acid (from step 2) (1.0 eq.) and 3-bromopicolino-nitrile (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. After workup, the crude product was suspended in hot toluene, centrifuged (2500 rpm, 5 min), and the supernatant was removed. The suspension, centrifugation, and removal of supernatant steps were repeated with hot ethyl acetate, ether, and hexane to give a pure solid. ^{1}H NMR (acetone *d*-6): δ 9.04 (d, 1H), 8.96 (d, 1H), 8.27 (d, 1H), 7.86-7.90 (dd, 1H), 7.28-7.34 (m, 2H), 6.9 (br, 2H). LRMS [M+H] = 214.1

Example 12

8-(methylsulfonyl)benzo[f][1,7]naphthyridin-5-amine



Step 1: 2-bromo-5-(methylsulfonyl)aniline

[000479] A solution of 1-bromo-4-(methylsulfonyl)-2-nitrobenzene (1.0 eq.), iron powder (3.0

eq.), and concentrated HCl (1.04 eq.) were mixed together in ethanol (0.64 M) and heated to reflux. The reaction was stirred for 24 hours, and the solvent was evaporated. The resulting residue was diluted with ethyl acetate and saturated aqueous ammonium chloride solution. The aqueous layer was extracted three times with ethyl acetate, and the combined organic layers were washed with water, brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by triturating in 1:1 hexane/ether to give a light yellow solid.

Step 2: tert-butyl 2-bromo-5-(methylsulfonyl)phenylcarbamate

[000480] To a solution of 2-bromo-5-(methylsulfonyl)aniline (from step 1) (1.0 eq.) in tetrahydrofuran (0.2 M) at 0°C under N_2 atmosphere was added dropwise 1M NaHMDS (2.5 eq.). The reaction was stirred for 15 minutes at 0°C, and a solution of di-*tert*-butyl dicarbonate in tetrahydrofuran was added. The reaction was warmed to room temperature overnight. The solvent was evaporated, and the resulting residue was quenched with 0.1N HCl aqueous solution. The aqueous suspension was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% ethyl acetate in hexane to give *tert*-butyl 2-bromo-5-(methylsulfonyl)phenylcarbamate.

Step 3: tert-butyl 5-(methylsulfonyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate

[000481] *Tert*-butyl 2-bromo-5-(methylsulfonyl)phenylcarbamate (from step 2) (1.0 eq.), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.5 eq.), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) (5%), and sodium acetate (4.5 eq.) were mixed in dioxane (0.2 M) under N_2 atmosphere. The reaction was heated to 100°C and stirred overnight. The resulting suspension was cooled to ambient temperature, diluted with ether, filtered through celite, and the filtrate was concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-50% ethyl acetate in hexane to give a solid which was then triturated in 10% ether/hexane to give *tert*-butyl 5-(methylsulfonyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate as a white solid.

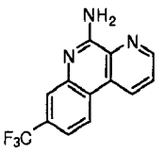
Step 4: 8-(methylsulfonyl)benzo[f][1,7]naphthyridin-5-amine

[000482] A solution of *tert*-butyl 5-(methylsulfonyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate(from step 3) (1.0 eq.) and 3-bromopicolino-nitrile (1.0 eq.) in toluene (0.24 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (4.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted

twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% methanol in dichloromethane to give a solid which was then triturated in 1:1 hexane/ethyl acetate to give 8-(methylsulfonyl)benzo[f][1,7]naphthyridin-5-amine. ^{1}H NMR (acetone *d*-6): δ 9.16 (d, 1H), 9.03 (d, 1H), 8.71 (d, 1H), 8.11 (s, 1H), 7.93-7.96 (dd, 1H), 7.81 (d, 1H), 7.0 (br, 2H), 3.19 (s, 3H). LRMS [M+H] = 274.1

Example 13

8-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine



Step 1: tert-butyl 2-bromo-5-(trifluoromethyl)phenylcarbamate

[000483] To a solution of 2-bromo-5-(trifluoromethyl)aniline (1.0 eq.) in tetrahydrofuran (0.2 M) at 0°C under N_2 atmosphere was added dropwise 1M NaHMDS (2.5 eq.). The reaction was stirred for 15 minutes at 0°C, and a solution of di-*tert*-butyl dicarbonate in tetrahydrofuran was added. The reaction was warmed to room temperature overnight. The solvent was evaporated, and the resulting residue was quenched with 0.1N HCl aqueous solution. The aqueous suspension was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% ethyl acetate in hexane to give product as light yellow oil.

Step 2: tert-butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenylcarbamate

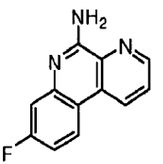
[000484] *Tert*-butyl 2-bromo-5-(trifluoromethyl)phenylcarbamate (from step 1) (1.0 eq.), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.5 eq.), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) (5%), and sodium acetate (4.5 eq.) were mixed in dioxane (0.2 M) under N_2 atmosphere. The reaction was heated to 100°C and stirred overnight. The resulting suspension was cooled to ambient temperature, diluted with ether, filtered through celite, and the filtrate was concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-10% ether in hexane to give an impure product which was carried onto the next step without further purification.

Step 3: 8-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine

[000485] A solution of *tert*-butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenylcarbamate (from step 2) (1.0 eq.) and 3-bromopicolino-nitrile (1.0 eq.) in toluene (0.24 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (4.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-40% ethyl acetate in toluene to give a solid which was then triturated in 10% ethyl acetate in hexane to give 8-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine. ^{1}H NMR (acetone *d*-6): δ 9.13 (d, 1H), 9.00 (d, 1H), 8.67 (d, 1H), 7.91-7.94 (dd, 1H), 7.86 (s, 1H), 7.58 (d, 1H), 6.9 (br, 2H). LRMS [M+H] = 264.1

Example 14

8-fluorobenzo[f][1,7]naphthyridin-5-amine



Step 1: tert-butyl 2-bromo-5-fluorophenylcarbamate

[000486] To a solution of 2-bromo-5-fluoroaniline (1.0 eq.) in tetrahydrofuran (0.2 M) at 0°C under N_2 atmosphere was added dropwise 1M NaHMDS (2.5 eq.). The reaction was stirred for 15 minutes at 0°C, and a solution of di-*tert*-butyl dicarbonate in tetrahydrofuran was added. The reaction was warmed to room temperature overnight. The solvent was evaporated, and the resulting residue was quenched with 0.1N HCl aqueous solution. The aqueous suspension was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% ethyl acetate in hexane to give the product as light yellow oil.

Step 2: tert-butyl 5-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate

[000487] *Tert*-butyl 2-bromo-5-fluorophenylcarbamate (from step 1) (1.0 eq.), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.5 eq.), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) (5%), and sodium acetate (4.5 eq.) were mixed in

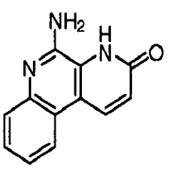
dioxane (0.2 M) under N_2 atmosphere. The reaction was heated to 100°C and stirred overnight. The resulting suspension was cooled to ambient temperature, diluted with ether, filtered through celite, and the filtrate was concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% ether in hexane to give the product as a yellow solid.

Step 3: 8-fluorobenzo[f][1,7]naphthyridin-5-amine

[000488] A solution of *tert*-butyl 5-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from step 2) (1.0 eq.) and 3-bromopicolino-nitrile (1.0 eq.) in toluene (0.24 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (4.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-40% ethyl acetate in toluene to give a solid which was then triturated in 10% ethyl acetate in hexane to give 8-fluorobenzo[f][1,7]naphthyridin-5-amine. ^{1}H NMR (acetone *d*-6): δ 9.00 (d, 1H), 8.90 (d, 1H), 8.46-8.50 (dd, 1H), 7.83-7.87 (dd, 1H), 7.26 (d, 1H), 7.15 (t, 1H), 6.9 (br, 2H). LRMS [M+H] = 214.1

Example 15

5-aminobenzo[f][1,7]naphthyridin-3(4H)-one



Step 1: 3-bromo-2-cyanopyridine 1-oxide

[000489] To a solution of 3-bromopicolinonitrile (1.0 eq.) in chloroform (0.3 M) was added 77% meta-chloroperbenzoic acid (mCPBA) (1.8 eq.) and heated at 60°C for 2 days. After cooling to room temperature, $Ca(OH)_2$ (2.5 eq.) was added, and the resulting precipitate was stirred for 30 minutes. The precipitate was filtered and washed with 5% methanol in dichloromethane. The filtrate was washed with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted several times with 3% methanol in dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *en vacuo*. The crude product was stirred in hot hexane/ethyl acetate (1:1), filtered, and dried to give the desired product as a white solid.

Step 2: 3-bromo-6-oxo-1,6-dihydropyridine-2-carbonitrile

[000490] A solution of 3-bromo-2-cyanopyridine 1-oxide (from step 1) in acetic anhydride (0.5 M) was heated at 150°C for 24 hours. The reaction was cooled to room temperature, and the solvent was removed *en vacuo*. The residue was purified by a COMBIFLASH® system (ISCO) using 0-90% ethyl acetate in hexane to give the O-acetate which was hydrolyzed in 2N NaOH / methanol (1:1, 0.2 M) at room temperature for 2 hours. The resulting mixture was diluted with water and acidified with 5% citric acid. The pale yellow precipitate was filtered and washed with 9:1 hexane/ethyl acetate and ether to give 3-bromo-6-oxo-1,6-dihydropyridine-2-carbonitrile.

Step 3: 3-bromo-6-(tert-butyldimethylsilyloxy)picolinonitrile

[000491] A solution of 3-bromo-6-oxo-1,6-dihydropyridine-2-carbonitrile (from step 2) (1.0 eq.), tert-butyldimethylsilylchloride (TBSCl) (1.8 eq.), and imidazole (2.5 eq.) in DMF (0.2 M) was heated to 60°C and stirred overnight. The reaction mixture was diluted with water and extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *en vacuo*. The residue was purified by a COMBIFLASH® system (ISCO) using 0-20% ethyl acetate in hexane to give 3-bromo-6-(*tert*-butyldimethylsilyloxy)picolinonitrile.

Step 4: 3-(tert-butyldimethylsilyloxy)benzo[f][1,7]naphthyridin-5-amine

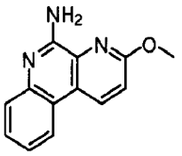
[000492] A solution of 2-(*tert*-butoxycarbonylamino)phenylboronic acid (1.0 eq.) and 3-bromo-6-(*tert*-butyldimethylsilyloxy)picolinonitrile (from step 3) (1.0 eq.) in toluene/ethanol (10:1, 0.2 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-50% ethyl acetate in hexane to give a solid.

Step 5: 5-aminobenzo[f][1,7]naphthyridin-3(4H)-one

[000493] To a solution of 3-(*tert*-butyldimethylsilyloxy)benzo[f][1,7]naphthyridin-5-amine (from step 4) (1.0 eq.) in tetrahydrofuran (0.05 M) was added tetra-n-butylammonium fluoride (TBAF) (1.0 eq.) and acetic acid (1.0 eq.). The reaction was stirred for 15 minutes, and then concentrated *en vacuo*. The crude residue was suspended in water and neutralized by addition of saturated aqueous $NaHCO_3$ solution to pH 7. The solids were filtered, washed with acetone, and dried to give 5-aminobenzo[f][1,7]naphthyridin-3(4H)-one. ^1H NMR (DMSO *d*-6): δ 8.59 (d, 1H), 8.20 (d, 1H), 7.49 (d, 1H), 7.37-7.41 (dd, 1H), 7.23-7.27 (dd, 1H), 6.88 (br, 2H), 6.79 (d, 1H).

LRMS [M+H] = 212.1

Example 16
3-methoxybenzo[f][1,7]naphthyridin-5-amine



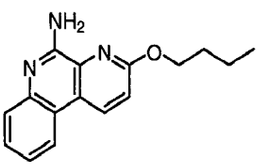
Step 1: 3-bromo-6-methoxypicolinonitrile

[000494] A solution of 3-bromo-6-oxo-1,6-dihydropyridine-2-carbonitrile (from Example 15 / Step 2) (1.0 eq.), silver carbonate (1.3 eq.), and iodomethane (1.2 eq.) in toluene (0.2 M) was stirred in the dark at room temperature overnight. The solvent was concentrated *en vacuo*, and the resulting residue was purified by a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give 3-bromo-6-methoxypicolinonitrile.

Step 2: 3-methoxybenzo[f][1,7]naphthyridin-5-amine

[000495] A solution of 2-(*tert*-butoxycarbonylamino)phenylboronic acid (1.0 eq.) and 3-bromo-6-methoxypicolinonitrile (from step 1) (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-50% ethyl acetate in hexane to give 3-methoxybenzo[f][1,7]naphthyridin-5-amine as a yellow solid. ^{1}H NMR (acetone *d*-6): δ 8.91 (d, 1H), 8.34 (d, 1H), 7.63 (d, 1H), 7.51-7.53 (dd, 1H), 7.27-7.33 (m, 2H), 6.65 (br, 2H), 4.11 (s, 3H). LRMS [M+H] = 226.1

Example 17
3-butoxybenzo[f][1,7]naphthyridin-5-amine



Step 1: 3-bromo-6-butoxypicolinonitrile

[000496] A solution of 3-bromo-6-oxo-1,6-dihydropyridine-2-carbonitrile (from Example 15 / Step 2) (1.0 eq.), potassium carbonate (1.3 eq.), and 1-iodobutane (1.2 eq.) in acetone (0.3 M) was

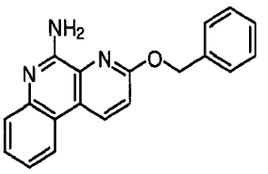
stirred at 70°C overnight. The solvent was concentrated *en vacuo*, and the resulting residue was taken up in water and ethyl acetate. The aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by a COMBIFLASH® system (ISCO) using 0-30% ethyl acetate in hexane to give a colorless solid.

Step 2: 3-butoxybenzo[f][1,7]naphthyridin-5-amine

[000497] A solution of 2-(*tert*-butoxycarbonylamino)phenylboronic acid (1.0 eq.) and 3-bromo-6-butoxypicolinonitrile (from step 1) (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% ethyl acetate in methanol to give 3-butoxybenzo[f][1,7]naphthyridin-5-amine as a white solid. ^{1}H NMR (acetone *d*-6): δ 8.91 (d, 1H), 8.34 (d, 1H), 7.61 (d, 1H), 7.48-7.52 (dd, 1H), 7.27-7.33 (m, 2H), 6.51 (br, 2H), 6.55 (t, 2H), 1.81-1.88 (m, 2H), 1.50-1.59 (m, 2H), 1.00 (t, 3H). LRMS [M+H] = 268.1

Example 18

3-(benzyloxy)benzo[f][1,7]naphthyridin-5-amine



Step 1: 6-(benzyloxy)-3-bromopicolinonitrile

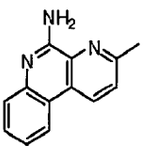
[000498] A solution of 3-bromo-6-oxo-1,6-dihydropyridine-2-carbonitrile (from Example 15 / Step 2) (1.0 eq.), silver carbonate (1.3 eq.), and benzyl bromide (1.2 eq.) in toluene (0.16 M) was stirred in the dark at 50°C overnight. The solvent was concentrated *en vacuo*, and the resulting residue was purified by a COMBIFLASH® system (ISCO) using 0-20% ethyl acetate in hexane to give 6-(benzyloxy)-3-bromopicolinonitrile.

Step 2: 3-(benzyloxy)benzo[f][1,7]naphthyridin-5-amine

[000499] A solution of 2-(*tert*-butoxycarbonylamino)phenylboronic acid (1.0 eq.) and 6-(benzyloxy)-3-bromopicolinonitrile (from step 1) (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution

(2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-50% ethyl acetate in hexane to give 3-(benzyloxy)benzo[f][1,7]naphthyridin-5-amine as a yellow solid. ^{1}H NMR (acetone *d*-6): δ 8.95 (d, 1H), 8.35 (d, 1H), 7.58-7.63 (m, 2H), 7.49-7.53 (dd, 1H), 7.30-7.44 (m, 5H), 6.61 (br, 2H), 5.64 (s, 2H). LRMS [M+H] = 302.1

Example 19
3-methylbenzo[f][1,7]naphthyridin-5-amine



Step 1: 5-bromo-2-methylpyridine 1-oxide

[000500] To a solution of 5-bromo-2-methylpyridine (1.0 eq.) in chloroform (0.38 M) was added 77% meta-chloroperbenzoic acid (mCPBA) (4.0 eq.) and heated at 60°C for 20 hours. After cooling to room temperature, $Ca(OH)_2$ (5.3 eq.) was added, and the resulting precipitate was stirred for 30 minutes. The precipitate was filtered and washed with 3:1 $CHCl_3$/methanol. The filtrate was concentrated *en vacuo* to give a solid, which was stirred in 30% ethyl acetate in hexane and filtered to give the desired N-oxide. The filtrate was concentrated *en vacuo*, and the residue was purified by a COMBIFLASH® system (ISCO) using 0-100% ethyl acetate in hexane to give more of the desired N-oxide. The two batches were combined and carried onto the next step.

Step 2: 3-bromo-6-methylpicolinonitrile

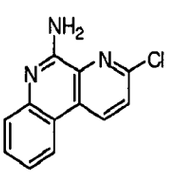
[000501] To a solution of 5-bromo-2-methylpyridine 1-oxide (from step 1) (1.0 eq.) in acetonitrile (0.2 M) was added trimethylsilyl cyanide (TMSCN) (4.0 eq.) and triethylamine (3.0 eq.). The reaction was heated at 100°C overnight. After cooling to room temperature, the solvent was concentrated en vacuo, and the residue was purified by a COMBIFLASH® system (ISCO) using 0-50% ethyl acetate in hexane to give 3-bromo-6-methylpicolinonitrile.

Step 3: 3-methylbenzo[f][1,7]naphthyridin-5-amine

[000502] A solution of 2-(*tert*-butoxycarbonylamino)phenylboronic acid (1.0 eq.) and 3-bromo-6-methylpicolinonitrile (from step 2) (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution

(2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-70% ethyl acetate in hexane to give 3-methylbenzo[f][1,7]naphthyridin-5-amine as a yellow solid. ^{1}H NMR (methanol *d*-4): δ 8.85 (d, 1H), 8.38 (d, 1H), 7.72 (d, 1H), 7.53-7.61 (m, 2H), 7.34-7.38 (dd, 1H), 2.76 (s, 3H). LRMS [M+H] = 210.1

Example 20
3-chlorobenzo[f][1,7]naphthyridin-5-amine



Step 1: 5-bromo-2-chloropyridine 1-oxide

[000503] To a solution of 5-bromo-2-chloropyridine (1.0 eq.) in chloroform (0.38 M) was added 77% meta-chloroperbenzoic acid (mCPBA) (4.0 eq.) and heated at 60°C for 20 hours. After cooling to room temperature, $Ca(OH)_2$ (5.3 eq.) was added, and the resulting precipitate was stirred for 30 minutes. The precipitate was filtered and washed with 3:1 $CHCl_3$/methanol. The filtrate was concentrated *en vacuo* to give a solid, which was stirred in 30% ethyl acetate in hexane and filtered to give the desired N-oxide. The filtrate was concentrated *en vacuo*, and the residue was purified by a COMBIFLASH® system (ISCO) using 0-100% ethyl acetate in hexane to give more of the desired N-oxide. The two batches were combined and carried onto the next step.

Step 2: 3-bromo-6-chloropicolinonitrile

[000504] To a solution of 5-bromo-2-chloropyridine 1-oxide (from step 1) (1.0 eq.) in acetonitrile (0.2 M) was added trimethylsilyl cyanide (TMSCN) (4.0 eq.) and triethylamine (3.0 eq.). The reaction was heated at 100°C overnight. After cooling to room temperature, the solvent was concentrated en vacuo, and the residue was purified by a COMBIFLASH® system (ISCO) using 0-40% ethyl acetate in hexane to give 3-bromo-6-chloropicolinonitrile.

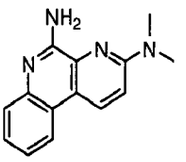
Step 3: 3-chlorobenzo[f][1,7]naphthyridin-5-amine

[000505] A solution of 2-(*tert*-butoxycarbonylamino)phenylboronic acid (1.0 eq.) and 3-bromo-6-chloropicolinonitrile (from step 2) (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution

(2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-50% ethyl acetate in hexane to give a solid, which was then triturated in 10% ethyl acetate in hexane to give 3-chlorobenzo[f][1,7]naphthyridin-5-amine. ^{1}H NMR (acetone *d*-6): δ 9.10 (d, 1H), 8.45 (d, 1H), 7.89 (d, 1H), 7.58-7.65 (m, 2H), 7.35-7.39 (dd, 1H), 6.67 (br, 2H). LRMS [M+H] = 230.1

Example 21

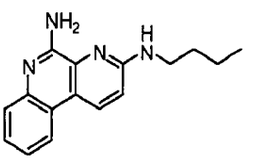
N^3,N^3-dimethylbenzo[f][1,7]naphthyridine-3,5-diamine



[000506] A solution of 3-chlorobenzo[f][1,7]naphthyridin-5-amine (Example 20) (1.0 eq.) was dissolved in 40% aqueous dimethylamine (0.26 M) and heated in a microwave reactor at 100°C for 30 minutes. The reaction mixture was concentrated *en vacuo*, and the residue was purified by a COMBIFLASH® system (ISCO) using 0-90% ethyl acetate in hexane to give N^3,N^3-dimethylbenzo[f][1,7]naphthyridine-3,5-diamine. ^{1}H NMR (methanol *d*-4): δ 8.63 (d, 1H), 8.20 (d, 1H), 7.55 (d, 1H), 7.41-7.45 (dd, 1H), 7.29-7.33 (dd, 1H), 7.27 (d, 1H), 3.26 (s, 6H). LRMS [M+H] = 239.1

Example 22

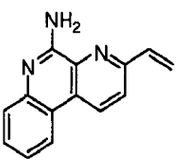
N^3-butylbenzo[f][1,7]naphthyridine-3,5-diamine



[000507] A solution of 3-chlorobenzo[f][1,7]naphthyridin-5-amine (Example 20) (1.0 eq.) was dissolved in *n*-butylamine (0.1 M) and heated at 110°C overnight. The reaction mixture was concentrated *en vacuo*, and the residue was purified by a COMBIFLASH® system (ISCO) using 0-90% ethyl acetate in hexane to give N^3-butylbenzo[f][1,7]naphthyridine-3,5-diamine. ^{1}H NMR (methanol *d*-4): δ 8.42 (d, 1H), 8.13 (d, 1H), 7.53 (d, 1H), 7.38-7.42 (dd, 1H), 7.25-7.29 (dd, 1H), 6.96 (d, 1H), 3.48 (t, 2H), 1.63-1.71 (m, 2H), 1.43-1.52 (m, 2H), 0.99 (t, 3H). LRMS [M+H] =

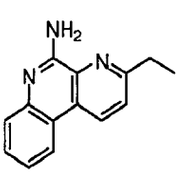
267.2

Example 23
3-vinylbenzo[f][1,7]naphthyridin-5-amine



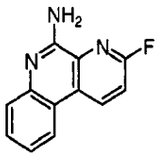
[000508] A solution of 3-chlorobenzo[f][1,7]naphthyridin-5-amine (Example 20) (1.0 eq.), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.2 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous potassium carbonate solution (2.0 eq.) in toluene/ethanol (4:1, 0.1 M) was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with ethyl acetate and water. The two phases were separated, and the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-50% ethyl acetate in hexane to give a solid, which was then triturated in 10% ethyl acetate in hexane to give 3-vinylbenzo[f][1,7]naphthyridin-5-amine. ^{1}H NMR (acetone *d*-6): δ 8.99 (d, 1H), 8.42 (d, 1H), 8.01 (d, 1H), 7.53-7.62 (m, 2H), 7.30-7.35 (dd, 1H), 7.03-7.10 (dd, 1H), 6.77 (br, 2H), 6.56 (d, 1H), 5.66 (d, 1H). LRMS [M+H] = 222.1

Example 24
3-ethylbenzo[f][1,7]naphthyridin-5-amine



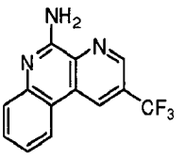
[000509] To a solution of 3-vinylbenzo[f][1,7]naphthyridin-5-amine (Example 23) in ethyl acetate/ethanol (1:1, 0.07 M) was added 10% wt palladium on carbon (0.2 eq.). Hydrogen gas was introduced via a balloon, and the reaction was stirred overnight. The mixture was filtered through a pad of celite, washing with dichloromethane. The filtrate was concentrated *en vacuo* giving 3-ethylbenzo[f][1,7]naphthyridin-5-amine as a white solid. ^{1}H NMR (acetone *d*-6): δ 8.93 (d, 1H), 8.41 (d, 1H), 7.76 (d, 1H), 7.61 (d, 1H), 7.51-7.55 (dd, 1H), 7.30-7.34 (dd, 1H), 6.55 (br, 2H), 6.03 (q, 2H), 1.41 (t, 3H). LRMS [M+H] = 224.1

Example 25
3-fluorobenzo[f][1,7]naphthyridin-5-amine



[000510] A solution of 3-chlorobenzo[f][1,7]naphthyridin-5-amine (Example 20) (1.0 eq.), potassium fluoride (3.0 eq.), and 18-crown-6 (0.2 eq.) in N-methylpyrrolidone (NMP) (0.4 M) was heated in a microwave reactor at 210°C for 80 minutes. After cooling to room temperature, the crude reaction mixture was purified by HPLC using 10-50% acetonitrile in water to give 3-fluorobenzo[f][1,7]naphthyridin-5-amine. ^{1}H NMR (acetone *d*-6): δ 11.40 (br, 2H), 9.38-9.42 (dd, 1H), 8.60 (d, 1H), 7.89-7.92 (dd, 1H), 7.81-7.83 (m, 2H), 7.59-7.66 (m, 1H). LRMS [M+H] = 214.1

Example 26
2-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine



Step 1: 3-chloro-5-(trifluoromethyl)picolinaldehyde oxime

[000511] A solution of 3-chloro-5-(trifluoromethyl)picolinaldehyde (1.0 eq.), hydroxylamine hydrochloride (5.0 eq.), and pyridine (4.0 eq.) in ethanol was heated to 95°C and stirred for 1 hour. The reaction was cooled to room temperature and diluted with ethyl acetate and water. The organic layer was washed with brine, water, dried over anhydrous $MgSO_4$, and concentrated *en vacuo* to give a solid that was carried onto the next step without further purification.

Step 2: 3-chloro-5-(trifluoromethyl)picolinonitrile

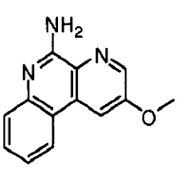
[000512] A solution of 3-chloro-5-(trifluoromethyl)picolinaldehyde oxime (1.0 eq.) and Burgess reagent (1.5 eq.) in tetrahydrofuran (0.5 M) was heated to 65°C and stirred for 1 hour. The reaction was cooled to room temperature and diluted with ethyl acetate and water. The organic layer was washed with water, brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo* to give a solid that was carried onto the next step without further purification.

Step 3: 2-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine

[000513] A solution of 2-(*tert*-butoxycarbonylamino)phenylboronic acid (1.0 eq.) and 3-chloro-5-(trifluoromethyl)picolinonitrile (from step 2) (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water.

The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-50% ethyl acetate in hexane to give 2-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine. ^1H NMR (acetone *d*-6): δ 9.44 (s, 1H), 9.20 (s, 1H), 8.65-8.63 (d, 1H), 7.70-7.61 (m, 2H), 7.44-7.36 (m, 1H), 6.84 (br, 2H). LRMS [M+H] = 264.2

Example 27
2-methoxybenzo[f][1,7]naphthyridin-5-amine



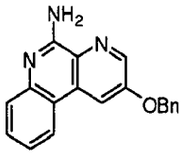
Step 1: 3-chloro-5-methoxypicolinonitrile

[000514] To a solution of 3,5-dichloropicolinonitrile (1.0 eq.) in dimethyl formamide (DMF) (0.5 M) was added sodium methoxide (1.5 eq.) and heated to 75°C. After stirring for 14 hours, the reaction was diluted with ethyl acetate and water. The organic layer was washed with saturated aqueous $NaHCO_3$ three times, water twice, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude residue was purified by a COMBIFLASH® system (ISCO) using 15% ethyl acetate in hexane to give a mixture of two methoxy regioisomers, one of which was the desired product. The mixture was carried onto the next step without further purification.

Step 2: 2-methoxybenzo[f][1,7]naphthyridin-5-amine

[000515] A solution of 2-(*tert*-butoxycarbonylamino)phenylboronic acid (1.0 eq.) and 3-chloro-5-methoxypicolinonitrile (from step 1) (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 50-100% ethyl acetate in hexane to give 2-methoxybenzo[f][1,7]naphthyridin-5-amine.

Example 28
2-(benzyloxy)benzo[f][1,7]naphthyridin-5-amine



Step 1: 3-(benzyloxy)-5-bromopyridine

[000516] A solution of 5-bromopyridin-3-ol (1.0 eq.), benzyl bromide (1.2 eq.), and silver carbonate (1.3 eq.) in toluene (0.1 M) was heated to 50°C and stirred for 18 hours. After cooling to room temperature, the reaction mixture was filtered, eluting with ethyl acetate. The filtrate was concentrated *en vacuo* into a residue that was purified by a COMBIFLASH® system (ISCO) using 20% ethyl acetate in hexane to give 3-(benzyloxy)-5-bromopyridine.

Step 2: 3-(benzyloxy)-5-bromopyridine 1-oxide

[000517] A solution of 3-(benzyloxy)-5-bromopyridine (from step 1) (1.0 eq.) and meta-chloroperbenzoic acid (mCPBA) (4.0 eq.) in dichloromethane (0.1 M) was stirred at room temperature for 18 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane three times. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *en vacuo*. The crude residue was purified by a COMBIFLASH® system (ISCO) using 0-100% ethyl acetate in hexane to give 3-(benzyloxy)-5-bromopyridine 1-oxide.

Step 3: 5-(benzyloxy)-3-bromopicolinonitrile

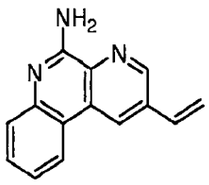
[000518] To a solution of 53-(benzyloxy)-5-bromopyridine 1-oxide (from step 2) (1.0 eq.) in acetonitrile (0.2 M) was added trimethylsilyl cyanide (TMSCN) (4.0 eq.) and triethylamine (3.0 eq.). The reaction was heated at 100°C overnight. After cooling to room temperature, the solvent was concentrated en vacuo, and the residue was purified by a COMBIFLASH® system (ISCO) using 0-40% ethyl acetate in hexane to give a mixture of two benzoxy regioisomers, one of which was the desired product. The mixture was carried onto the next step without further purification.

Step 4: 2-(benzyloxy)benzo[f][1,7]naphthyridin-5-amine

[000519] A solution of 2-(*tert*-butoxycarbonylamino)phenylboronic acid (1.0 eq.) and 5-(benzyloxy)-3-bromopicolinonitrile (from step 3) (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction content was diluted with 2% methanol in dichloromethane and water. The two phases were separated, and the aqueous layer was extracted twice with 2% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 50-100% ethyl acetate in hexane to give 2-

(benzyloxy)benzo[f][1,7]naphthyridin-5-amine. ^{1}H NMR (acetone *d*-6): δ 8.36 (s, 1H), 7.86 (s, 1H), 7.59-7.56 (d, 2H), 7.46-7.42 (dd, 2H), 7.40-7.37 (d, 1H), 7.20-7.15 (dd, 1H), 7.12-7.09 (d, 1H), 6.88-6.86 (d, 1H), 6.77-6.73 (dd, 1H), 5.51 (s, 2H), 4.74 (br, 2H). LRMS [M+H] = 302.3.

Example 29
2-vinylbenzo[f][1,7]naphthyridin-5-amine



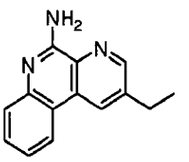
Step 1: 3-chloro-5-vinylpicolinonitrile

[000520] A solution of 3,5-dichloropicolinonitrile (1.0 eq.), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (3.4 eq.) in toluene/ethanol (2:1, 0.04 M) was stirred at 95°C overnight. After cooling to ambient temperature, the reaction content was diluted with ethyl acetate and water. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give a white solid.

Step 2: 2-vinylbenzo[f][1,7]naphthyridin-5-amine

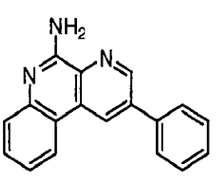
[000521] A solution of 2-(*tert*-butoxycarbonylamino)phenylboronic acid (1.0 eq.) and 3-chloro-5-vinylpicolinonitrile (from step 1) (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (2.0 eq.) in toluene/ethanol (2:1, 0.03 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction content was diluted with methanol. The insoluble solids were filtered off, and the filtrate was concentrated *en vacuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give 2-vinylbenzo[f][1,7]naphthyridin-5-amine as a yellow solid. ^{1}H NMR (methanol-*d*4 – $CDCl_3$): δ 8.87 (d, 1H), 8.69 (d, 1H), 8.28 (d, 1H), 7.49-7.58 (m, 2H), 7.32 (dt, 1H), 6.90 (dd, 1H), 6.09 (d, 1H), 5.54 (d, 1H). LRMS [M+H] = 222.1.

Example 30
2-ethylbenzo[f][1,7]naphthyridin-5-amine



[000522] To a solution of 2-vinylbenzo[f][1,7]naphthyridin-5-amine (Example 29) in ethyl acetate/methanol (1:4, 0.05 M) was added 10% wt palladium on carbon (0.2 eq.). Hydrogen gas was introduced via a balloon, and the reaction was stirred for 3 hours. The mixture was filtered through a pad of celite, washing with dichloromethane. The filtrate was concentrated *en vacuo* and purified by a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give 2-ethylbenzo[f][1,7]naphthyridin-5-amine as a solid. ^{1}H NMR (methanol-d4): δ 8.78-8.81 (m, 2H), 8.45 (d, 1H), 7.55 – 7.63 (m, 2H), 7.35 - 7.40 (m, 1H), 2.97 (q, 2H), 1.43 (t, 2H). LRMS [M+H] = 224.1.

Example 31
2-phenylbenzo[f][1,7]naphthyridin-5-amine



Step 1: 3-chloro-5-phenylpicolinonitrile

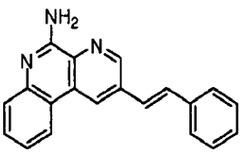
[000523] A solution of 3,5-dichloropicolinonitrile (1.0 eq.), 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (3.4 eq.) in toluene/ethanol (2:1, 0.04 M) was stirred at 100°C for 2 hours, then 80°C for 4 hours. After cooling to ambient temperature, the reaction content was diluted with ethyl acetate and water. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give a white solid.

Step 2: 2-phenylbenzo[f][1,7]naphthyridin-5-amine

[000524] A solution of 2-(*tert*-butoxycarbonylamino)phenylboronic acid (1.0 eq.) and 3-chloro-5-phenylpicolinonitrile (from step 1) (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (2.0 eq.) in toluene/ethanol (2:1, 0.03 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction content was diluted with methanol. The insoluble solids were filtered off, and the filtrate was concentrated *en vacuo* to obtain a crude residue. The crude product was purified by flash chromatography on a

COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give 2-phenylbenzo[f][1,7]naphthyridin-5-amine as a white solid. ^{1}H NMR (dmso-d6): δ 9.13 (d, 1H), 9.03 (d, 1H), 8.56 (d, 1H), 7.98 (d, 2H), 7.43- 7.56 (m, 5H), 7.27 (m, 1H), 7.13 (bs, 2H). LRMS [M+H] = 272.2.

Example 32
(E)-2-styrylbenzo[f][1,7]naphthyridin-5-amine



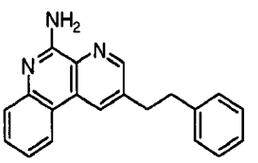
Step 1: (E)-3-chloro-5-styrylpicolinonitrile

[000525] A solution of 3,5-dichloropicolinonitrile (1.0 eq.), (E)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (3.4 eq.) in toluene/ethanol (2:1, 0.04 M) was stirred at 100°C for 2 hours, then 80°C for 4 hours. After cooling to ambient temperature, the reaction content was diluted with ethyl acetate and water. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give a white solid.

Step 2: (E)-2-styrylbenzo[f][1,7]naphthyridin-5-amine

A solution of 2-(tert-butoxycarbonylamino)phenylboronic acid (1.0 eq.) and (E)-3-chloro-5-styrylpicolinonitrile (from step 1) (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (2.0 eq.) in toluene/ethanol (2:1, 0.03 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction content was diluted with methanol. The insoluble solids were filtered off, and the filtrate was concentrated *en vacuo* to obtain a crude residue. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give (E)-2-styrylbenzo[f][1,7]naphthyridin-5-amine as a brown solid. ^{1}H NMR (dmso-d6): δ 9.22 (d, 1H), 9.06 (d, 1H), 8.51 (d, 1H), 7.78 (d, 1H), 7.66 (d, 2H), 7.46- 7.56 (m, 3H), 7.70 (t, 2H), 7.26- 7.32 (m, 2H), 7.08 (bs, 2H). LRMS [M+H] = 298.2.

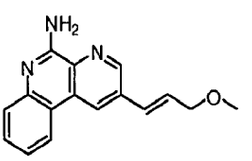
Example 33
2-phenethylbenzo[f][1,7]naphthyridin-5-amine



[000526] To a solution of (E)-2-styrylbenzo[f][1,7]naphthyridin-5-amine (Example 32) in ethyl acetate/methanol (1:4, 0.05 M) was added 10% wt palladium on carbon (0.2 eq.). Hydrogen gas was introduced via a balloon, and the reaction was stirred for 3 hours. The mixture was filtered through a pad of celite, washing with dichloromethane. The filtrate was concentrated *en vacuo* and the crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give 2-phenethylbenzo[f][1,7]naphthyridin-5-amine as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.54 (d, 1H), 8.32 (d, 1H), 8.10 (dd, 1H), 7.63 (dd, 1H), 7.51 (m, 1H), 7.03 – 7.32 (m, 6H), 6.16 (bs, 2H), 3.11 (t, 2H), 2.97 (t, 2H). LRMS [M+H] = 300.1.

Example 34

(E)-2-(3-methoxyprop-1-enyl)benzo[f][1,7]naphthyridin-5-amine



Step 1: (E)-3-chloro-5-(3-methoxyprop-1-enyl)picolinonitrile

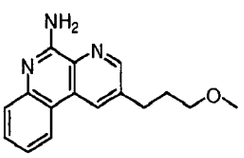
[000527] A solution of 3,5-dichloropicolinonitrile (1.0 eq.), (E)-2-(3-methoxyprop-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (3.4 eq.) in toluene/ethanol (2:1, 0.04 M) was stirred at 100°C for 2 hours, then 80°C for 4 hours. After cooling to ambient temperature, the reaction content was diluted with ethyl acetate and water. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give (E)-3-chloro-5-(3-methoxyprop-1-enyl)picolinonitrile as a white solid.

Step 2: (E)-2-(3-methoxyprop-1-enyl)benzo[f][1,7]naphthyridin-5-amine

[000528] A solution of 2-(*tert*-butoxycarbonylamino)phenylboronic acid (1.0 eq.) and (E)-3-chloro-5-(3-methoxyprop-1-enyl)picolinonitrile (from step 1) (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (2.0 eq.) in toluene/ethanol (2:1, 0.03 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction content was diluted with methanol. The insoluble solids were filtered

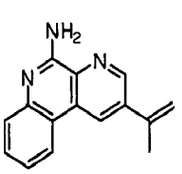
off, and the filtrate was concentrated *en vacuo* to obtain a crude residue. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give (E)-2-(3-methoxyprop-1-enyl)benzo[f][1,7]naphthyridin-5-amine as a yellow solid. ^{1}H NMR (dmso-d6): δ 9.24 (d, 1H), 9.18 (d, 1H), 8.54 (d, 1H), 7.52- 7.58 (m, 2H), 7.31 (m, 1H), 7.11 (bs, 2H), 6.86 – 7.00 (m, 2H), 4.18 (d, 2H), 3.36 (s, 3H). LRMS [M+H] = 266.2.

Example 35
2-(3-methoxypropyl)benzo[f][1,7]naphthyridin-5-amine



[000529] To a solution of (E)-2-(3-methoxyprop-1-enyl)benzo[f][1,7]naphthyridin-5-amine (Example 34) in ethyl acetate/methanol (1:4, 0.05 M) was added 10% wt palladium on carbon (0.2 eq.). Hydrogen gas was introduced via a balloon, and the reaction was stirred for 3 hours. The mixture was filtered through a pad of celite, washing with dichloromethane. The filtrate was concentrated *en vacuo* and the crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give 2-(3-methoxypropyl)benzo[f][1,7]naphthyridin-5-amine as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.64 (d, 1H), 8.46 (d, 1H), 8.19 (d, 1H), 7.66 (d, 1H), 7.53 (m, 1H), 7.31 (m, 1H), 6.56 (bs, 2H), 3.37 (t, 2H), 3.31 (s, 3H), 2.91 (t, 2H), 1.93 – 2.00 (m, 2H). LRMS [M+H] = 268.1.

Example 36
2-(prop-1-en-2-yl)benzo[f][1,7]naphthyridin-5-amine



Step 1: 3-chloro-5-(prop-1-en-2-yl)picolinonitrile

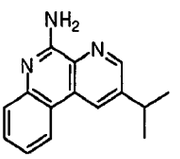
[000530] A solution of 3,5-dichloropicolinonitrile (1.0 eq.), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (3.4 eq.) in toluene/ethanol (2:1, 0.04 M) was stirred at 100°C for 2 hours, then 80°C for 4 hours. After cooling to ambient temperature, the reaction content was diluted with ethyl acetate and water. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to

give 3-chloro-5-(prop-1-en-2-yl)picolinonitrile as a white solid.

Step 2: 2-(prop-1-en-2-yl)benzo[f][1,7]naphthyridin-5-amine

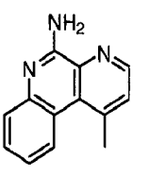
[000531] A solution of 2-(*tert*-butoxycarbonylamino)phenylboronic acid (1.0 eq.) and 3-chloro-5-(prop-1-en-2-yl)picolinonitrile (from step 1) (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (2.0 eq.) in toluene/ethanol (2:1, 0.03 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction content was diluted with methanol. The insoluble solids were filtered off, and the filtrate was concentrated *en vacuo* to obtain a crude residue. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give 2-(prop-1-en-2-yl)benzo[f][1,7]naphthyridin-5-amine as a white solid. ^{1}H NMR (dmso-d6): δ 9.03 (d, 1H), 8.96 (d, 1H), 8.55 (d, 1H), 7.47- 7.53 (m, 2H), 7.25 (m, 1H), 7.07 (bs, 2H) 5.80 (s, 1H), 5.36 (s, 1H), 2.27 (s, 3H). LRMS [M+H] = 236.2.

Example 37
2-isopropylbenzo[f][1,7]naphthyridin-5-amine



[000532] To a solution of 2-(prop-1-en-2-yl)benzo[f][1,7]naphthyridin-5-amine (Example 36) in ethyl acetate/methanol (1:4, 0.05 M) was added 10% wt palladium on carbon (0.2 eq.). Hydrogen gas was introduced via a balloon, and the reaction was stirred for 3 hours. The mixture was filtered through a pad of celite, washing with dichloromethane. The filtrate was concentrated *en vacuo* and the crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give 2-isopropylbenzo[f][1,7]naphthyridin-5-amine as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.69 (d, 1H), 8.49 (d, 1H), 8.25 (dd, 1H), 7.65 (dd, 1H), 7.53 (m, 1H), 7.31 (m, 1H), 6.02 (bs, 2H), 3.15 (septet, 1H), 1.37 (d, 6H). LRMS [M+H] = 238.2.

Example 38
1-methylbenzo[f][1,7]naphthyridin-5-amine



Step 1: 5-bromo-2-chloro-4-methylpyridine 1-oxide

[000533] A solution of 5-bromo-2-chloro-4-methylpyridine (1.0 eq.) and meta-chloroperbenzoic acid (mCPBA) (2.5 eq.) in chloroform (0.1 M) was stirred at 50°C overnight. After cooling to

room temperature, $Ca(OH)_2$ (2.5 eq.) was added to the reaction mixture. The precipitate was filtered and washed with 5% methanol in dichloromethane and ethyl acetate. The filtrate was washed with saturated aqueous $Na_2S_2O_3$ solution and saturated aqueous $NaHCO_3$ solution. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vacuo* into a pale solid that was carried onto the next step without further purification.

Step 2: 3-bromo-6-chloro-4-methylpicolinonitrile

[000534] To a solution of 5-bromo-2-chloro-4-methylpyridine 1-oxide (from step 1) (1.0 eq.) in acetonitrile (0.2 M) was added TMSCN (4.0 eq.) and triethylamine (3.0 eq.). The reaction was heated at 100°C overnight. After cooling to room temperature, the solvent was concentrated en vacuo, and the residue was purified by a COMBIFLASH® system (ISCO) using 0-50% ethyl acetate in hexane to give 3-bromo-6-chloro-4-methylpicolinonitrile.

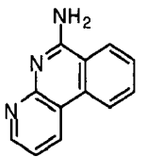
Step 3: 3-chloro-1-methylbenzo[f][1,7]naphthyridin-5-amine

[000535] A solution of 2-(*tert*-butoxycarbonylamino)phenylboronic acid (1.0 eq.) and 3-bromo-6-chloro-4-methylpicolinonitrile (from step 2) (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (2.0 eq.) in toluene/ethanol (2:1, 0.03 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction content was diluted with methanol. The insoluble solids were filtered off, and the filtrate was concentrated *en vacuo* to obtain a crude residue. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give 3-chloro-1-methylbenzo[f][1,7]naphthyridin-5-amine as a white solid. ^{1}H NMR (dmso-d6): δ 8.44 (d, 1H), 7.83 (s, 1H), 7.50- 7.58 (m, 2H), 7.02 (bs, 2H), 2.98 (s, 3H). LRMS [M+H] = 244.1.

Step 4: 1-methylbenzo[f][1,7]naphthyridin-5-amine

[000536] To a solution of 3-chloro-1-methylbenzo[f][1,7]naphthyridin-5-amine (from step 3) in ethyl acetate/methanol (1:2, 0.03 M) was added 10% wt palladium on carbon (0.2 eq.). The reaction vessel was shaken on a hydrogen Parr apparatus under 50 psi of hydrogen overnight. The mixture was filtered through a pad of celite, washing with dichloromethane. The filtrate was concentrated *en vacuo* and purified by a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give 1-methylbenzo[f][1,7]naphthyridin-5-amine as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.63 (d, 1H), 8.44 (d, 1H), 7.71 (dd, 1H), 7.54 (m, 1H), 7.45 (d, 1H), 7.30 (m, 1H), 6.20 (bs, 2H), 3.01 (s, 3H). LRMS [M+H] = 210.1.

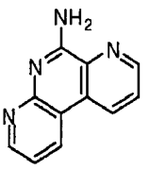
Example 39
benzo[c][1,8]naphthyridin-6-amine



[000537] A solution of tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-ylcarbamate (1.0 eq.) and 2-bromobenzonitrile (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (2.0 eq.) in toluene/ethanol (2:1, 0.03 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction content was diluted with methanol. The insoluble solids were filtered off, and the filtrate was concentrated *en vacuo* to obtain a crude residue. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give benzo[c][1,8]naphthyridin-6-amine as a white solid. ^{1}H NMR (methanol-d4): δ 8.88 (dd, 1H), 8.67-8.63 (m, 2H), 8.30 (d, 1H), 7.90 (dt, 1H), 7.74 (dt, 1H), 7.36 (dd, 1H). LRMS [M+H] = 196.1

Example 40

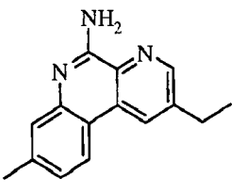
pyrido[3,2-f][1,7]naphthyridin-6-amine



[000538] A solution of tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-ylcarbamate (1.0 eq.) and 3-bromopicolinonitrile (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (2.0 eq.) in toluene/ethanol (2:1, 0.03 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction content was diluted with methanol. The insoluble solids were filtered off, and the filtrate was concentrated *en vacuo* to obtain a crude residue. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give pyrido[3,2-f][1,7]naphthyridin-6-amine as a white solid. ^{1}H NMR (dmso-d6): δ 9.14 (dd, 1H), 8.98 (dd, 1H), 8.90 (dd, 1H), 7.93 (dd, 1H), 7.60 (bs, 2H), 7.30 (dd, 1H). LRMS [M+H] = 197.

Example 41

2-ethyl-8-methylbenzo[f][1,7]naphthyridin-5-amine



Step 1: 8-methyl-2-vinylbenzo[f][1,7]naphthyridin-5-amine

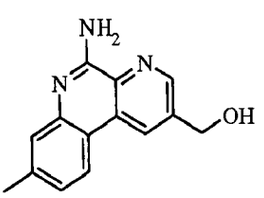
[000539] A solution of tert-butyl 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from Example 5/step 2) (1.0 eq.) and 3-chloro-5-vinylpicolinonitrile (from Example 29 / Step 1) (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (2.0 eq.) in toluene/ethanol (2:1, 0.03 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction content was diluted with methanol. The insoluble solids were filtered off, and the filtrate was concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give 8-methyl-2-vinylbenzo[f][1,7]naphthyridin-5-amine as a yellow solid.

Step 2: 2-ethyl-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000540] To a solution of 8-methyl-2-vinylbenzo[f][1,7]naphthyridin-5-amine (from the previous step) in ethyl acetate/methanol (1:4, 0.05 M) was added 10% wt palladium on carbon (0.2 eq.). Hydrogen gas was introduced via a ballon, and the reaction was stirred for 3 hours. The mixture was filtered through a pad of celite and washed with dichloromethane. The filtrate was concentrated *en vaccuo* and purified by a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give 2-ethyl-8-methylbenzo[f][1,7]naphthyridin-5-amine as an offwhite solid. ^{1}H NMR ($CDCl_3$): δ 8.61 (d, 1H), 8.42 (d, 1H), 8.10 (d, 1H), 7.44 (s, 1H), 7.12 (dd, 1H), 6.00 (bs, 2H), 2.84 (q, 2H), 2.45 (s, 3H), 1.33 (t, 3H). LRMS [M+H] = 238.1.

Example 42

(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)methanol



Step 1: ethyl 5-chloro-6-cyanonicotinate

[000541] A solution of ethyl 5,6-dichloronicotinate (1 eq), zinc cyanide (0.75 eq) and tetrakis(triphenyl-phosphine)palladium (0.10 eq.) in DMF (0.3 M) was degassed and then heated at 100 °C for 3 hours. Solvent was removed *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give ethyl 5-chloro-6-cyanonicotinate as a white solid.

Step 2: ethyl 5-amino-8-methylbenzo[f][1,7]naphthyridine-2-carboxylate

[000542] A solution of tert-butyl 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

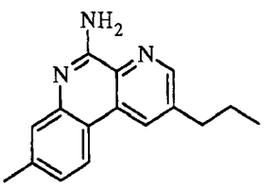
yl)phenylcarbamate (from Example 5 /step 2) (1.0 eq.) and ethyl 5-chloro-6-cyanonicotinate (from the previous step) (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (2.0 eq.) in toluene/ethanol (2:1, 0.03 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction content was diluted with methanol. The insoluble solids were filtered off, and the filtrate was concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give ethyl 5-amino-8-methylbenzo[f][1,7]naphthyridine-2-carboxylate.

Step 3: 2-ethyl-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000543] To a stirred solution of ethyl 5-amino-8-methylbenzo[f][1,7]naphthyridine-2-carboxylate (from the previous step) in THF (0.2 M) cooled in an ice-water bath was added 1 N solution of super hydride in THF (10 eq.). Upon completion of the reaction the reaction was quenched with 1 N HCl, and extracted with EtOAc. Combined organic extracts were concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)methanol as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.68 (d, 1H), 8.52 (d, 1H), 8.04 (d, 1H), 7.44 (s, 1H), 7.12 (dd, 1H), 6.00 (bs, 2H), 4.90 (s, 2H), 2.45 (s, 3H). LRMS [M+H] = 240.1

Example 43

8-methyl-2-propylbenzo[f][1,7]naphthyridin-5-amine



Step 1: (E)-3-chloro-5-(prop-1-enyl)picolinonitrile

[000544] A solution of 3,5-dichloropicolinonitrile (1.0 eq.), (E)-4,4,5,5-tetramethyl-2-(prop-1-enyl)-1,3,2-dioxaborolane (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (3.4 eq.) in toluene/ethanol (2:1, 0.04 M) was stirred at 95°C overnight. After cooling to ambient temperature, the reaction content was diluted with ethyl acetate and water. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated en vaccuo to obtain a crude residue. The crude material was purified by flash

chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give a white solid (E)-3-chloro-5-(prop-1-enyl)picolinonitrile.

Step 2: (E)-8-methyl-2-(prop-1-enyl)benzo[f][1,7]naphthyridin-5-amine

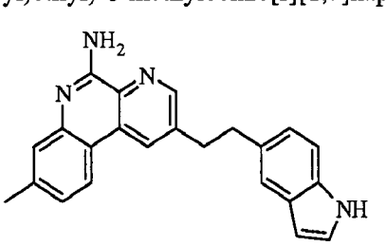
[000545] A solution of tert-butyl 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from Example 5 / Step 2) (1.0 eq.) and (E)-3-chloro-5-(prop-1-enyl)picolinonitrile (from the previous step) (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (2.0 eq.) in toluene/ethanol (2:1, 0.03 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction content was diluted with methanol. The insoluble solids were filtered off, and the filtrate was concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give (E)-8-methyl-2-(prop-1-enyl)benzo[f][1,7]naphthyridin-5-amine as a yellow solid.

Step 3: 8-methyl-2-propylbenzo[f][1,7]naphthyridin-5-amine

[000546] To a solution of (E)-8-methyl-2-(prop-1-enyl)benzo[f][1,7]naphthyridin-5-amine (from the previous step) in ethyl acetate/methanol (1:4, 0.05 M) was added 10% wt palladium on carbon (0.2 eq.). Hydrogen gas was introduced via a ballon, and the reaction was stirred for 3 hours. The mixture was filtered through a pad of celite, washing with dichloromethane. The filtrate was concentrated *en vaccuo* and purified by a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give 8-methyl-2-propylbenzo[f][1,7]naphthyridin-5-amine as offwhite solid. ^{1}H NMR ($CDCl_3$): δ 8.59 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.43 (s, 1H), 7.13 (dd, 1H), 5.94 (bs, 2H), 2.78 (t, 2H), 2.44 (s, 3H), 1.75 (m, 2H), 0.95 (t, 3H). LRMS [M+H] = 252.1

Example 44

2-(2-(1H-indol-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



Step 1: 5-((triethylsilyl)ethynyl)-1H-indole

[000547] To a scintillation vial was added -iodo-1H-indole (1.1 eq.), triethyl(ethynyl)silane (1 eq.), triethylamine (5 eq.), and anhydrous DMF (0.2 M). Vacuumed and nitrogen flushed for three times. CuI (0.1 eq.) and bis(triphenylphosphine)dichloro-palladium(II) (0.1 eq) were added. The vial was sealed and heated at 60 °C overnight. Upon completion of the reaction as monitored by

TLC, the content of the vial was loaded onto a silica gel column pretreated with hexanes. Column was washed with hexanes and diethylether until all eluents containing product were collected. Carefully distill off hexanes and ether using rotary evaporator with minim heating afforded product 5-((triethylsilyl)ethynyl)-1H-indole as colorless oil, which was carried directly on to the next step.

Step 2: 5-ethynyl-1H-indole

[000548] To a stirred solution of 5-((triethylsilyl)ethynyl)-1H-indole (from the previous step) in THF (0.2 M) cooled at 0 °C was treated with a solution (0.5 eq.) of tetrabutylammonium fluoride in a dropwise fashion. The reaction mixture turned black and was continued to stirr for 30 minutes before warming up to rt. TLC showed full conversion. The reaction was quenched with water and was extracted with diethylether. Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated using rotary evaporator with minim heating. Chromatography (silica gel, diethylether) afforded the product 5-ethynyl-1H-indole as colorless oil.

Step 3: 5-((1H-indol-5-yl)ethynyl)-3-chloropicolinonitrile

[000549] To a round bottom flask capped with septa was added 5-ethynyl-1H-indole (from the previous step) (1.1 eq), 3,5-dichloropicolinonitrile (1 eq.), triethylamine (5 eq.), and anhydrous DMF (0.2 M). Vacuumed and nitrogen flushed for three times. CuI (0.05 eq.) and bis(triphenylphosphine)dichloro-palladium(II) (0.05 eq) were added. The septum was replaced with a refluxing condenser and the flask was heated at 60 °C overnight under nitrogen atmosphere. Upon completion of the reaction as monitored by TLC, the content of the flask was loaded onto a large silica gel column pretreated with hexanes. Flash chromatography (silica gel, hexanes:EtOAc (1:4%)) afforded the product 5-((1H-indol-5-yl)ethynyl)-3-chloropicolinonitrile.

Step 4: 2-((1H-indol-5-yl)ethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000550] To a round bottom flask with refluxing condenser were added 5-((1H-indol-5-yl)ethynyl)-3-chloropicolinonitrile (from the previous step) (1 eq.), tert-butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from Example 5 / Step 2) (1.25 eq.), K_3PO_4 (2 eq.), tris(dibenzylideneacetone)dipalladium(0) (0.05 eq.), and 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.1 eq.). n-Butanol and water (5:2, 0.2 M) were added, and the content were degassed (vacuum followed by nitrogen flush) for three times. The reaction mixture was stirred vigorously under nitrogen at 100 °C overnight in an oil bath. The content were cooled down and were taken up in 200 mL of water followed by extraction with methylene chloride. Combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, 0 – 50%

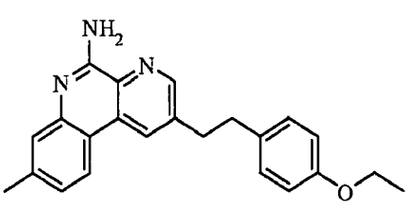
EtOAc in CH_2Cl_2) afforded the product 2-((1H-indol-5-yl)ethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine as a yellow solid.

Step 5: 2-(2-(2,3-dihydrobenzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000551] To a round bottom flask was added 2-((1H-indol-5-yl)ethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine (from the previous step) (1 eq.) with a stirring bar. Ethanol and methylene chloride (1:2, 0.2 M) were added, followed by palladium in carbon (activated powder, wet, 10% on carbon, 0.1 eq.). The content were vacuumed followed by hydrogen flush for three times. The reaction mixture was stirred vigorously under hydrogen balloon at room temperature overnight. Afterwards the reaction mixture was filtered through a celite pad, and the celite pad was washed subsequently with methylene chloride and EtOAc until the filtrate had no UV absorption. Combined organic washes were concentrated. Flash chromatography (silica gel, 0 – 50% EtOAc in CH_2Cl_2) afforded the product 2-(2-(2,3-Dihydrobenzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine as a yellow solid. ^1H NMR ($CDCl_3$): δ 8.54 (d, 1H), 8.34 (d, 1H), 8.28 (s, 1H), 7.99 (d, 1H), 7.64 – 7.56 (m, 1H), 7.50 – 7.35 (m, 1H), 7,24 (d, 1H), 7.12 (t, 1H), 7.08 (dd, 1H), 6.92 (dd, 1H), 6.41 (s, 1H), 6.01 (bs, 2H), 3.16 – 3.12 (m, 2H), 3.10 – 3.05 (m, 2H), 2.43 (s, 3H). LRMS [M+H] = 353.2

Example 45

2-(4-ethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



Step 1: 3-chloro-5-((4-ethoxyphenyl)ethynyl)picolinonitrile

[000552] To a round bottom flask capped with septa was added 1-ethoxy-4-ethynylbenzene (1.1 eq), 3,5-dichloropicolinonitrile (1 eq.), triethylamine (5 eq.), and anhydrous DMF (0.2 M). Vacuumed and nitrogen flushed for three times. CuI (0.05 eq.) and bis(triphenylphosphine)dichloro-palladium(II) (0.05 eq) were added. The septum was replaced with a refluxing condenser and the flask was heated at 60 °C overnight under nitrogen atmosphere. Upon completion of the reaction as monitored by TLC, the content of the flask was loaded onto a large silica gel column pretreated with hexanes. Flash chromatography (silica gel, hexanes:EtOAc (1:4%)) afforded the product 3-chloro-5-((4-ethoxyphenyl)ethynyl)picolinonitrile.

Step 2: 2-((4-ethoxyphenyl)ethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

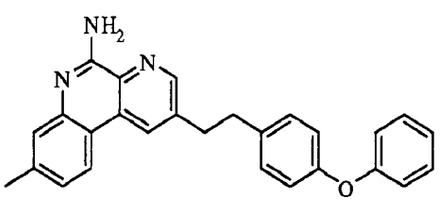
[000553] To a round bottom flask with refluxing condenser were added 3-chloro-5-((4-ethoxyphenyl)ethynyl)picolinonitrile (from the previous step) (1 eq.), tert-butyl 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from Example 5 / Step 2) (1.25 eq.), K_3PO_4 (2 eq.), tris(dibenzylideneacetone)dipalladium(0) (0.05 eq.), and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.1 eq.). n-Butanol and water (5:2, 0.2 M) were added, and the content were degassed (vacuum followed by nitrogen flush) for three times. The reaction mixture was stirred vigorously under nitrogen at 100 °C overnight in an oil bath. The content were cooled down and were taken up in 200 mL of water followed by extraction with methylene chloride. Combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, 0 – 50% EtOAc in CH_2Cl_2) afforded the product 2-((4-ethoxyphenyl)ethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine.

Step 3: 2-(4-ethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000554] To a round bottom flask was added 2-((4-ethoxyphenyl)ethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine (from the previous step) (1 eq.) with a stirring bar. Ethanol and methylene chloride (1:2, 0.2 M) were added, followed by palladium in carbon (activated powder, wet, 10% on carbon, 0.1 eq.). The contents were degassed under vacuum followed by hydrogen flush (three times). The reaction mixture was stirred vigorously under hydrogen balloon at room temperature overnight. Afterwards the reaction mixture was filtered through a celite pad, and the celite pad was washed subsequently with methylene chloride and EtOAc until the filtrate had no UV absorption. Combined organic washes were concentrated. Flash chromatography (silica gel, 0 – 50% EtOAc in CH_2Cl_2) afforded the product as a yellow solid. Further recrystalization using toluene afforded product 2-(4-ethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine as a white fine crystal. ^1H NMR ($CDCl_3$): δ 8.52 (d, 1H), 8.30 (d, 1H), 8.10 (d, 1H), 7.46 (s, 1H), 7.12 (dd, 1H), 7.06 (d, 2H), 6.75 (d, 2H), 5.95 (bs, 2H), 3.93 (q, 2H), 3.11 – 3.05 (dd, 2H), 2.95 – 2.90 (dd, 2H), 2.44 (s, 3H), 1.33 (t, 3H). LRMS [M+H] = 358.2

Example 46

8-methyl-2-(4-phenoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine



Step 1: 3-chloro-5-((4-phenoxyphenyl)ethynyl)picolinonitrile

[000555] 3-Chloro-5-((4-phenoxyphenyl)ethynyl)picolinonitrile was prepared from 1-ethynyl-4-phenoxybenzene (commercially available) following the procedures described for Example 45, step 1.

Step 2: 8-methyl-2-((4-phenoxyphenyl)ethynyl)benzo[f][1,7]naphthyridin-5-amine

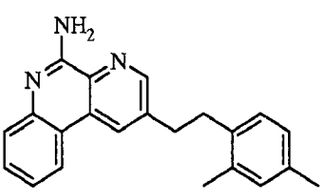
[000556] 8-Methyl-2-((4-phenoxyphenyl)ethynyl)benzo[f][1,7]naphthyridin-5-amine was prepared from 3-chloro-5-((4-phenoxyphenyl)ethynyl)picolinonitrile (from the previous step) following the procedures described for Example 45, step 2.

Step 3: 8-methyl-2-(4-phenoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine

[000557] 8-Methyl-2-(4-phenoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine was prepared from 8-methyl-2-((4-phenoxyphenyl)ethynyl)benzo[f][1,7]naphthyridin-5-amine (from the previous step) following the procedures described for Example 45, step 3. ^{1}H NMR ($CDCl_3$): δ 8.54 (d, 1H), 8.30 (d, 1H), 8.01 (d, 1H), 7.45 (s, 1H), 7.25 – 7.20 (m, 2H), 7.12 (dd, 1H), 7.07 – 6.84 (m, 8H), 6.00 (bs, 2H), 3.13 – 3.08 (dd, 2H), 2.99 – 2.94 (dd, 2H), 2.44 (s, 3H). LRMS [M+H] = 406.2

Example 47

2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine



Step 1: ((2,4-dimethylphenyl)ethynyl)triethylsilane

[000558] ((2,4-Dimethylphenyl)ethynyl)triethylsilane was prepared from 1-iodo-2,4-dimethylbenzene (commercially available) following the procedures described for Example 44, step 1.

Step 2: 1-ethynyl-2,4-dimethylbenzene

[000559] 1-Ethynyl-2,4-dimethylbenzene was prepared from ((2,4-dimethylphenyl)ethynyl)triethylsilane (from the previous step) following the procedures described for Example 44, step 2.

Step 3: 3-chloro-5-((2,4-dimethylphenyl)ethynyl)picolinonitrile

[000560] 3-Chloro-5-((2,4-dimethylphenyl)ethynyl)picolinonitrile was prepared from 1-ethynyl-2,4-dimethylbenzene (from the previous step) following the procedures described for Example 44, step 3.

Step 4: 2-((2,4-dimethylphenyl)ethynyl)benzo[f][1,7]naphthyridin-5-amine

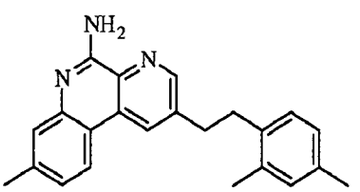
[000561] 2-((2,4-Dimethylphenyl)ethynyl)benzo[f][1,7]naphthyridin-5-amine was prepared from 3-chloro-5-((2,4-dimethylphenyl)ethynyl)-picolinonitrile (from the previous step) following the procedures described for Example 44, step 4.

Step 5: 2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine

[000562] 2-(2,4-Dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine was prepared from 2-((2,4-dimethylphenyl)ethynyl)benzo[f][1,7]naphthyridin-5-amine (from the previous step) following the procedures described for Example 44, step 5. ^{1}H NMR ($CDCl_3$): δ 8.60 (d, 1H), 8.33 (d, 1H), 8.14 (d, 1H), 7.67 (d, 1H), 7.54 (t, 1H), 7.31 (t, 1H), 6.96 – 6.86 (m, 3H), 6.29 (bs, 2H), 3.04 – 3.10 (dd, 2H), 2.97 – 2.91 (dd, 2H), 2.24 (s, 3H), 2.20 (s, 3H). LRMS [M+H] = 328.2.

Example 48

2-(2,4-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



Step 1: 2-((2,4-dimethylphenyl)ethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

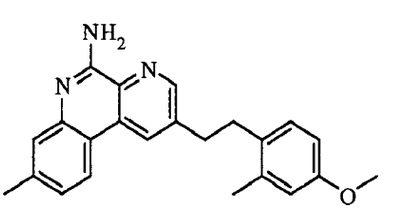
[000563] 2-((2,4-Dimethylphenyl)ethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared from 3-chloro-5-((2,4-dimethylphenyl)ethynyl)picolinonitrile (from Example 47 / Step 3) and tert-butyl 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from Example 5 / Step 2) following the procedures described for Example 44, step 4.

Step 2: 2-(2,4-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000564] 2-(2,4-Dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared from 1-ethynyl-4-phenoxybenzene (from the previous step) following the procedures described for Example 44, step 5. ^{1}H NMR ($CDCl_3$): δ 8.56 (d, 1H), 8.28 (d, 1H), 8.00 (d, 1H), 7.46 (s, 1H), 7.14 (dd, 1H), 6.95 – 6.85 (m, 3H), 6.26 (bs, 2H), 3.08 – 3.02 (dd, 2H), 2.96 – 2.90 (dd, 2H), 2.45 (s, 3H), 2.23 (s, 3H), 2.19 (s, 3H). LRMS [M+H] = 342.2

Example 49

2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



Step 1: 3-chloro-5-((4-methoxy-2-methylphenyl)ethynyl)picolinonitrile

[000565] 3-Chloro-5-((4-methoxy-2-methylphenyl)ethynyl)picolinonitrile was prepared from 1-ethynyl-4-methoxy-2-methylbenzene (commercially available) following the procedure described for Example 44 / Step 3.

Step 2: 2-((4-methoxy-2-methylphenyl)ethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

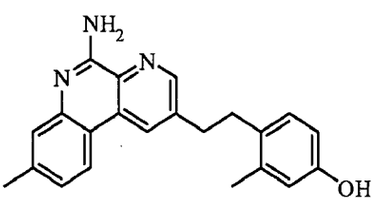
[000566] 2-((4-Methoxy-2-methylphenyl)ethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared from 3-chloro-5-(4-methoxy-2-methylphenethyl)picolinonitrile (from the previous step) following the procedures described for Example 44, step 4.

Step 3: 2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000567] 2-(4-Methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared from 2-((4-methoxy-2-methylphenyl)ethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine (from the previous step) following the procedures described for Example 44, step 5. ^{1}H NMR ($CDCl_3$): δ 8.53 (d, 1H), 8.29 (d, 1H), 8.01 (d, 1H), 7.44 (s, 1H), 7.12 (dd, 1H), 6.93 (d, 1H), 6.67 (d, 1H), 6.60 (dd, 1H), 5.93 (bs, 2H), 3.70 (s, 3H), 3.05 – 3.00 (dd, 2H), 2.93 – 2.88 (dd, 2H), 2.44 (s, 3H), 2.19 (s, 3H). LRMS [M+H] = 358.2

Example 50

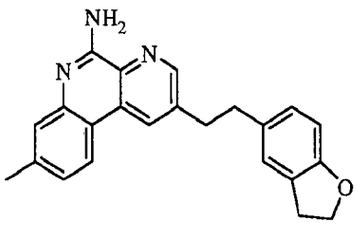
4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol



[000568] To a stirred solution of 2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine (Example 49) in methylene chloride (0.2 M) in an ice-water bath was added 1 N solution of BBr_3 (2 eq) in CH_2Cl_2 in a drop-wise fashion. In 30 minutes the reaction was quenched with methanol and was concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-20% methanol in dichloromethane to give 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol as a white solid. ^{1}H NMR (DMSO-d_6): δ 8.99 (s, 1H), 8.75 (d, 1H), 8.60 (d, 1H), 8.27 (d, 1H), 7.28 (s, 1H), 7.09 (dd, 1H), 6.99 (bs, 2H), 6.88 (d, 1H), 6.49 (d, 1H), 6.42 (dd, 1H), 3.02 – 2.96 (dd, 2H), 2.86 – 2.81 (dd, 2H), 2.38 (s, 3H), 2.13 (s, 3H). LRMS [M+H] = 344.2

Example 51

2-(2-(2,3-dihydrobenzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



Step 1: ((2,3-dihydrobenzofuran-5-yl)ethynyl)triethylsilane

[000569] ((2,3-Dihydrobenzofuran-5-yl)ethynyl)triethylsilane was prepared from 5-iodo-2,3-dihydrobenzofuran (commercially available) following the procedures described for Example 44, step 1.

Step 2: 5-ethynyl-2,3-dihydrobenzofuran

[000570] 5-Ethynyl-2,3-dihydrobenzofuran was prepared from ((2,3-dihydrobenzofuran-5-yl)ethynyl)triethylsilane (from the previous step) following the procedures described for Example 44 / Step 2.

Step 3: 3-chloro-5-((2,3-dihydrobenzofuran-5-yl)ethynyl)picolinonitrile

[000571] 3-Chloro-5-((2,3-dihydrobenzofuran-5-yl)ethynyl)picolinonitrile was prepared from 5-ethynyl-2,3-dihydrobenzofuran (from the previous step) following the procedures described for Example 44 / Step 3.

Step 4: 2-((2,3-dihydrobenzofuran-5-yl)ethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

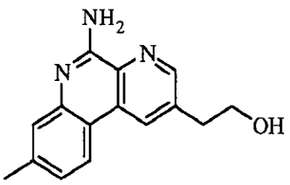
[000572] 2-((2,3-Dihydrobenzofuran-5-yl)ethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared from 3-chloro-5-(4-methoxy-2-methylphenethyl)picolinonitrile (from the previous step) following the procedures described for Example 44 / Step 4.

Step 5: 2-(2-(2,3-dihydrobenzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000573] 2-(2-(2,3-Dihydrobenzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared from 2-((2,3-dihydrobenzofuran-5-yl)ethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine (from the previous step) following the procedures described for Example 44 / Step 5. ^{1}H NMR ($CDCl_3$): δ 8.62 (d, 1H), 8.40 (d, 1H), 8.11 (d, 1H), 7.53 (s, 1H), 7.21 (dd, 1H), 6.99 (s, 1H), 6.95 (dd, 1H), 6.74 (d, 1H), 6.05 (bs, 2H), 4.57 (t, 2H), 3.19 – 3.13 (m, 4H), 3.03 – 2.98 (dd, 2H), 2.54 (s, 3H). LRMS [M+H] = 356.2

Example 52

2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethanol



Step 1: (Z)-3-chloro-5-(2-ethoxyvinyl)picolinonitrile

[000574] (Z)-3-Chloro-5-(2-ethoxyvinyl)picolinonitrile was prepared from (Z)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (commercially available) following the procedures described for Example 43 / Step 1.

Step 2: (Z)-2-(2-ethoxyvinyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

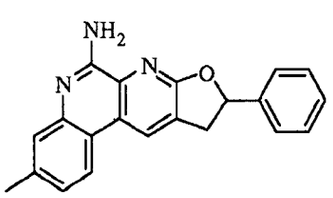
[000575] (Z)-2-(2-Ethoxyvinyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared from (Z)-3-chloro-5-(2-ethoxyvinyl)picolinonitrile (from the previous step) following the procedures described for Example 43 / Step 2.

Step 3: 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethanol

[000576] A solution of (Z)-2-(2-ethoxyvinyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine (from the previous step) in a mixture of 2:5 conc. HCl and dioxane (0.1 M) was heated at 60 °C overnight. Upon cooling down to rt, the reaction mixture was treated with excess $NaHCO_3$ saturated solution, followed by extraction with EtOAc. Combined organic extracts were concentrated and was taken up in THF (0.2 M), and was treated with 1 N super hydride solution in THF (10 eq.) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was worked up following the procedures described for Example 42 / Step 3, to afford 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethanol as white solid. ^1H NMR ($CDCl_3$): δ 8.61 (d, 1H), 8.47 (d, 1H), 8.01 (d, 1H), 7.41 (s, 1H), 7,10 (d, 1H), 6.40 (s, 1H), 6.01 (bs, 2H), 4.01 (t, 2H), 3.06 (t, 2H), 2.43 (s, 3H). LRMS [M+H] = 254.1

Example 53

3-methyl-9-phenyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine



Step 1: 5-bromo-2-chloro-3-methylpyridine 1-oxide

[000577] 5-Bromo-2-chloro-3-methylpyridine 1-oxide was prepared from 5-bromo-2-chloro-3-methylpyridine (commercially available) following the procedures described for Example 19 / Step 1.

Step 2: 3-bromo-6-chloro-5-methylpicolinonitrile

[000578] 3-Bromo-6-chloro-5-methylpicolinonitrile was prepared from (Z)-3-chloro-5-(2-ethoxyvinyl)picolinonitrile (from the previous step) following the procedures described for Example 19 / Step 2.

Step 3: 3-bromo-6-chloro-5-(2-hydroxy-2-phenylethyl)picolinonitrile

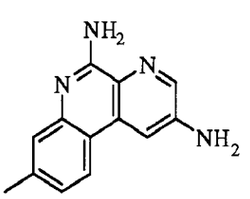
[000579] A solution of 3-bromo-6-chloro-5-methylpicolinonitrile (from the previous step) in THF (0.2 M) was cooled to -78 °C. LDA (2N solution, 2 eq) was added dropwise. The reaction was kept stirring at -78 °C for 1 hour, followed by addition of benzaldehyde (1 eq). The reaction was kept stirring at -78 °C for another 30 minutes before allowing it to slowly warm to room temperature. The reaction was quenched with sat. NH_4Cl and extracted with EtOAc. Combined organic washes were concentrated. Flash chromatography (silica gel, 20 – 50% EtOAc in hexanes) afforded the product 3-bromo-6-chloro-5-(2-hydroxy-2-phenylethyl)picolinonitrile as a yellow solid.

Step 4: 3-methyl-9-phenyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine

[000580] 3-Methyl-9-phenyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine was prepared from 3-bromo-6-chloro-5-methylpicolinonitrile (from the previous step) following the procedures described for Example 44 / Step 4. ^1H NMR ($CDCl_3$): δ 8.45 (s, 1H), 7.98 (d, 1H), 7.45 (s, 1H), 7.40 – 7.28 (m, 5H), 7.12 (d, 1H), 5.93 (t, 1H), 5.93 (brs, 2H), 3.86 (dd, 1H), 3.40 (dd, 1H), 2.44 (s, 3H). LRMS [M+H] = 328.1

Example 54

8-methylbenzo[f][1,7]naphthyridine-2,5-diamine



Step 1: tert-butyl 5,6-dichloropyridin-3-ylcarbamate

[000581] To a solution of 5,6-dichloropyridin-3-amine (commercially available) in THF (0.2 M) stirred at 0 °C was added $(BOC)_2O$ (1.2 eq). The reaction mixture was heated at 40 °C until full conversion as monitored by TLC. The reaction mixture was then concentrated. Flash chromatography (silica gel, 20 – 50% EtOAc in hexanes) of the crude afforded tert-butyl 5,6-dichloropyridin-3-ylcarbamate.

Step 2: tert-butyl 5-chloro-6-cyanopyridin-3-ylcarbamate

[000582] Tert-butyl 5-chloro-6-cyanopyridin-3-ylcarbamate was prepared from tert-butyl 5,6-dichloropyridin-3-ylcarbamate (from the previous step) following the procedures described for

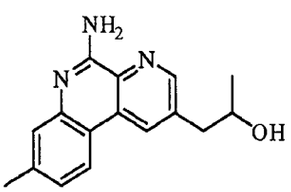
Example 42 / Step 1.

Step 3: 8-methylbenzo[f][1,7]naphthyridine-2,5-diamine

[000583] 8-methylbenzo[f][1,7]naphthyridine-2,5-diamine was prepared (as minor product) together with tert-butyl 5-amino-8-methylbenzo[f][1,7]naphthyridin-2-ylcarbamate (as major product) from tert-butyl 5-chloro-6-cyanopyridin-3-ylcarbamate (from the previous step) following the procedures described for Example 5 / Step 2. ^{1}H NMR (DMSO-d_6): δ 10.11 (s, 1H), 9.02 (s, 1H), 8.82 (d, 1H), 8.06 (d, 1H), 7.34 (s, 1H), 7,15 (dd, 1H), 6.99 (s, 2H), 2.44 (s, 3H). LRMS [M+H] = 225.1

Example 55

1-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)propan-2-ol



Step 1: 3-bromo-5-methylpicolinonitrile

[000584] 3-Bromo-5-methylpicolinonitrile was prepared from 2,3-dibromo-5-methylpyridine (commercially available) following the procedures described for Example 42 / Step 1.

Step 2: 3-bromo-5-(2-hydroxypropyl)picolinonitrile

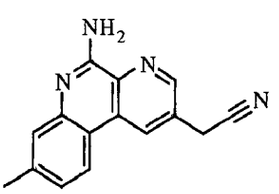
[000585] 3-Bromo-5-(2-hydroxypropyl)picolinonitrile was prepared from 3-bromo-5-methylpicolinonitrile (from the previous step) and acetaldehyde following the procedures described for Example 53 / Step 3.

Step 3: 1-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)propan-2-ol

[000586] 1-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)propan-2-ol was prepared from 3-bromo-5-(2-hydroxypropyl)picolinonitrile (from the previous step) following the procedures described for Example 53, step 4. ^{1}H NMR (methanol-d_4): δ 8.72 (d, 1H), 8.68 (d, 1H), 8.24 (d, 1H), 7.38 (s, 1H), 7,18 (dd, 1H), 4.16 – 4.07 (m, 1H), 3.05 – 2.99 (m, 2H), 2.97 – 2.90 (m, 2H), 2.47 (s, 3H), 1.28 (d, 3H). LRMS [M+H] = 268.1

Example 56

2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetonitrile



Step 1: 2,3-dichloro-5-((methoxymethoxy)methyl)pyridine

[000587] To a stirred solution of (5,6-dichloropyridin-3-yl)methanol (commercially available) in CH_2Cl_2 (0.2 M) at 0 °C was added triethylamine (3 eq.) and chloro(methoxy)methane (2 eq.). After stirring at 0 °C for 3 hours the reaction mixture was concentrated and the crude was purified by chromatography (silica gel, 20 – 50% EtOAc in hexanes) to afford 2,3-dichloro-5-((methoxymethoxy)methyl)pyridine as a colorless oil.

Step 2: 3-chloro-5-((methoxymethoxy)methyl)picolinonitrile

[000588] 3-Chloro-5-((methoxymethoxy)methyl)picolinonitrile was prepared from 2,3-dichloro-5-((methoxymethoxy)methyl)pyridine (from the previous step) following the procedures described for Example 42 / Step 1.

Step 3: 3-chloro-5-(hydroxymethyl)picolinonitrile

[000589] To a stirred solution of 2,3-dichloro-5-((methoxymethoxy)methyl)pyridine (from the previous step) in methanol (0.2 M) was added conc. HCl (10 eq). After stirring at room temperature overnight the reaction mixture was concentrated under vacuum and the resulting crude was purified by chromatography (silica gel, 20 – 50% EtOAc in hexanes) to afford 3-chloro-5-(hydroxymethyl)picolinonitrile.

Step 4: 3-chloro-5-(chloromethyl)picolinonitrile

[000590] To a stirred solution of 3-chloro-5-(hydroxymethyl)picolinonitrile (from the previous step) in CH_2Cl_2 (0.2 M) at 0 °C was added thionyl chloride (10 eq). After stirring at room temperature overnight the reaction mixture was concentrated under vacuum and the resulting crude was purified by chromatography (silica gel, 20 – 50% EtOAc in hexanes) to afford 3-chloro-5-(chloromethyl)picolinonitrile as a colorless oil.

Step 5: 3-chloro-5-(cyanomethyl)picolinonitrile

[000591] To a solution of 3-chloro-5-(chloromethyl)picolinonitrile (from the previous step) in DMSO (0.2 M) was added sodium cyanide (1.25 eq). The reaction mixture was heated at 130 °C under microwave irradiation. The reaction mixture taken up in water and EtOAc, and extracted with EtOAc. Organic phases were dried over anhydrous Na_2SO_4, and concentrated. Flash chromatography (silica gel, 20 – 50% EtOAc in hexanes) of the crude afforded 3-chloro-5-(cyanomethyl)picolinonitrile.

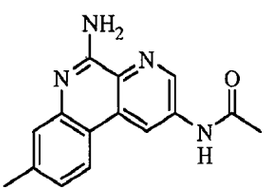
Step 6: 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetonitrile

[000592] 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetonitrile was prepared from 3-chloro-5-(cyanomethyl)picolinonitrile (from the previous step) following the procedures described

for Example 44 / Step 4. ^{1}H NMR (methanol-d_4): δ 8.79 (d, 1H), 8.78 (d, 1H), 8.20 (d, 1H), 7.66 (s, 2H), 7.36 (s, 1H), 7,18 (dd, 1H), 4.15 (d, 2H), 2.43 (s, 3H). LRMS [M+H] = 249.1

Example 57

N-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetamide



Step 1: N-(5,6-dichloropyridin-3-yl)acetamide

[000593] To a stirred solution of 5,6-dichloropyridin-3-amine (commercially available) and triethyl amine (3 eq) in CH_2Cl_2 (0.2 M) at 0 °C was added acetyl chloride (2 eq). After stirring at room temperature overnight the reaction mixture was concentrated under vacuum and the resulting crude residue was purified by chromatography (silica gel, 20 – 50% EtOAc in hexanes) to afford N-(5,6-dichloropyridin-3-yl)acetamide.

Step 2: N-(5-chloro-6-cyanopyridin-3-yl)acetamide

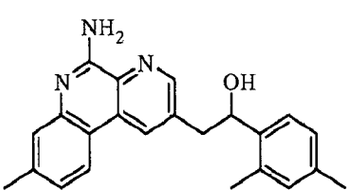
[000594] N-(5-chloro-6-cyanopyridin-3-yl)acetamide was prepared from N-(5,6-dichloropyridin-3-yl)acetamide (from the previous step) following the procedures described for Example 42 / Step 1.

Step 3: N-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetamide

[000595] N-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetamide was prepared from N-(5-chloro-6-cyanopyridin-3-yl)acetamide (from the previous step) following the procedures described for Example 44 / Step 4. ^{1}H NMR (DMSO-d_6): δ 10.99 (s, 1H), 8.18 (d, 1H), 8.95 (d, 1H), 8.12 (d, 1H), 7.44 (s, 1H), 7,35 (dd, 1H), 2.43 (s, 3H), 2.16 (s, 3H). LRMS [M+H] = 267.1

Example 58

2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(2,4-dimethylphenyl)ethanol



Step 1: 3-bromo-5-(2-(2,4-dimethylphenyl)-2-hydroxyethyl)picolinonitrile

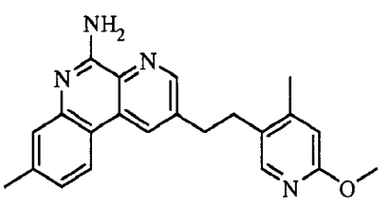
[000596] 3-bromo-5-(2-(2,4-dimethylphenyl)-2-hydroxyethyl)picolinonitrile was prepared from 3-bromo-5-methylpicolinonitrile (Example 55 / Step 1) and 2,4-dimethylbenzaldehyde following the procedures described for Example 53 / Step 3.

Step 2: 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(2,4-dimethylphenyl)ethanol

[000597] 2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(2,4-dimethylphenyl)ethanol was prepared from 3-bromo-5-(2-(2,4-dimethylphenyl)-2-hydroxyethyl)picolinonitrile (from the previous step) following the procedures described for Example 53 / Step 4. ^{1}H NMR ($CDCl_3$): δ 8.67 (d, 1H), 8.45 (d, 1H), 8.06 (d, 1H), 7.57 (s, 1H), 7.42 (d, 1H), 7.23 (d, 1H), 7.11 (d, 1H), 7.01 (s, 1H), 5.31(dd, 1H), 3.28 – 3.25 (m, 2H), 2.53 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H). LRMS [M+H] = 358.2

Example 59

2-(2-(6-methoxy-4-methylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



Step 1: 2-methoxy-4-methyl-5-((triethylsilyl)ethynyl)pyridine

[000598] 2-Methoxy-4-methyl-5-((triethylsilyl)ethynyl)pyridine was prepared from 5-bromo-2-methoxy-4-methylpyridine (commercially available) following the procedures described for Example 44 / Step 1.

Step 2: 5-ethynyl-2-methoxy-4-methylpyridine

[000599] 5-Ethynyl-2-methoxy-4-methylpyridine was prepared from 2-methoxy-4-methyl-5-((triethylsilyl)ethynyl)pyridine (from the previous step) following the procedures described for Example 44 / Step 2.

Step 3: 3-chloro-5-((6-methoxy-4-methylpyridin-3-yl)ethynyl)picolinonitrile

[000600] 3-Chloro-5-((6-methoxy-4-methylpyridin-3-yl)ethynyl)picolinonitrile was prepared from 5-ethynyl-2-methoxy-4-methylpyridine (from the previous step) following the procedures described for Example 44 / Step 3.

Step 4: 2-((6-methoxy-4-methylpyridin-3-yl)ethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000601] 2-((6-Methoxy-4-methylpyridin-3-yl)ethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared from 3-chloro-5-((6-methoxy-4-methylpyridin-3-yl)ethynyl)picolinonitrile (from the previous step) following the procedures described for Example 44 / Step 4.

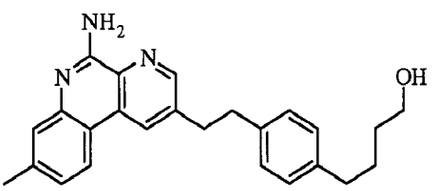
Step 5: 2-(2-(6-methoxy-4-methylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000602] 2-(2-(6-Methoxy-4-methylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared from 2-((6-methoxy-4-methylpyridin-3-yl)ethynyl)-8-

methylbenzo[f][1,7]naphthyridin-5-amine (from the previous step) following the procedures described for Example 44 / Step 5. ^{1}H NMR ($CDCl_3$): δ 8.65 (d, 1H), 8.43 (d, 1H), 8.13 (d, 1H), 7.87 (s, 1H), 7.57 (s, 1H), 7.24 (dd, 1H), 6.60 (s, 1H), 6.39 (bs, 2H), 3.91 (s, 3H),3.17 – 3.11 (dd, 2H), 3.03 – 2.98 (dd, 2H), 2.54 (s, 3H), 2.28 (s, 3H). LRMS [M+H] = 359.2

Example 60

4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)butan-1-ol



Step 1: 4-(4-((trimethylsilyl)ethynyl)phenyl)but-3-yn-1-ol

[000603] 4-(4-((trimethylsilyl)ethynyl)phenyl)but-3-yn-1-ol was prepared from ((4-bromophenyl)ethynyl)trimethylsilane (commercially available) and but-3-yn-1-ol (commercially available) following the procedures described for Example 44 / Step 1.

Step 2: 4-(4-ethynylphenyl)but-3-yn-1-ol

[000604] 4-(4-ethynylphenyl)but-3-yn-1-ol was prepared from 4-(4-((trimethylsilyl)ethynyl)phenyl)but-3-yn-1-ol following the procedures described for Example 44 / Step 2.

Step 3: 5-((4-(4-hydroxybut-1-ynyl)phenyl)ethynyl)-3-methylpicolinonitrile

[000605] 5-((4-(4-hydroxybut-1-ynyl)phenyl)ethynyl)-3-methylpicolinonitrile was prepared from 4-(4-ethynylphenyl)but-3-yn-1-ol (from the previous step) following the procedures described for Example 44 / Step 3.

Step 4: 4-(4-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)phenyl)but-2-yn-1-ol

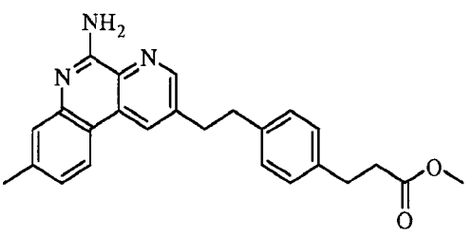
[000606] 4-(4-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)phenyl)but-2-yn-1-ol was prepared from 5-((4-(4-hydroxybut-1-ynyl)phenyl)ethynyl)-3-methylpicolinonitrile (from the previous step) following the procedures described for Example 44 / Step 4.

Step 5: 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)butan-1-ol

[000607] 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)butan-1-ol was prepared from 4-(4-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)phenyl)but-2-yn-1-ol (from the previous step) following the procedures described for Example 44 / Step 5. ^{1}H NMR ($CDCl_3$): δ 8.58 (d, 1H), 8.36 (d, 1H), 8.07 (d, 1H), 7.53 (s, 1H), 7.20 (dd, 1H), 7.10 (dd, 4H), 6.20 (bs, 2H), 3.68 (t, 2H), 3.20 – 3.15 (dd, 2H), 3.06 – 3.01 (dd, 2H), 2.64 (t, 2H), 2.52 (s, 3H), 1.75 – 1.57 (m, 4H). LRMS [M+H] = 386.2

Example 61

methyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoate



Step 1: methyl 3-(4-iodophenyl)propanoate

[000608] To a stirred solution of 3-(4-iodophenyl)propanoic acid (commercially available) in toluene and methanol (9:1, 0.2 M) 0 °C was added (diazomethyl)trimethylsilane (1 N solution in Et_2O, 2 eq). After stirring at room temperature overnight the reaction mixture was concentrated under vacuum and the resulting crude residue was purified by chromatography (silica gel, 20 – 50% EtOAc in hexanes) to afford methyl 3-(4-iodophenyl)propanoate.

Step 2: methyl 3-(4-ethynylphenyl)propanoate

[000609] Methyl 3-(4-ethynylphenyl)propanoate was prepared from methyl 3-(4-iodophenyl)propanoate (from the previous step) following the procedures described for Example 44 / Steps 1 and 2.

Step 3: methyl 3-(4-((5-chloro-6-cyanopyridin-3-yl)ethynyl)phenyl)propanoate

[000610] Methyl 3-(4-((5-chloro-6-cyanopyridin-3-yl)ethynyl)phenyl)propanoate was prepared from methyl 3-(4-ethynylphenyl)propanoate (from the previous step) following the procedures described for Example 44 / Step 3.

Step 4: methyl 3-(4-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)phenyl)propanoate

[000611] Methyl 3-(4-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)phenyl)propanoate was prepared from methyl 3-(4-((5-chloro-6-cyanopyridin-3-yl)ethynyl)phenyl)propanoate (from the previous step) following the procedures described for Example 44 / Step 4.

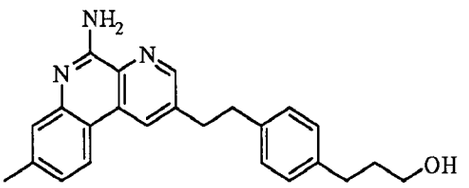
Step 5: methyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoate

[000612] Methyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoate was prepared from methyl 3-(4-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)phenyl)propanoate (from the previous step) following the procedures described for Example 44 / Step 5. ^{1}H NMR (DMSO-d_6): δ 8.83 (d, 1H), 8.72 (d, 1H), 8.32 (d, 1H), 7.35 (s, 1H), 7.21-7.12 (m, 5H), 7.05 (br s, 2H), 7.05 (dd, 2H), 3.57 (s, 3H), 3.19 – 3.13 (dd, 2H), 3.06 – 3.00 (dd, 2H), 2.81 (t, 2H), 2.60 (t, 2H), 2.45 (s, 3H). LRMS

[M+H] = 400.2

Example 62

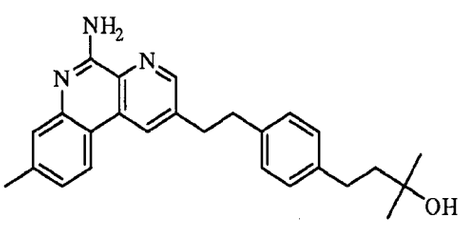
3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-1-ol



[000613] 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-1-ol was prepared from methyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoate (from Example 61) following the procedures described for Example 42/ Step 3. ^{1}H NMR **of the TFA salt**: (DMSO-d_6): δ 9.56 (s, 1H), 9.24 (s, 1H), 8.92 (d, 1H), 8.81 (d, 1H), 8.43 (d, 1H), 7.44 (d, 1H), 7.35 (d, 1H), 7.13 (dd, 2H), 7.05 (dd, 2H), 3.32 (t, 2H), 3.18 – 3.12 (dd, 2H), 3.02 – 2.95 (dd, 2H), 2.50 (t, 2H), 2.44 (s, 3H), 1.65 – 1.57 (m, 2H). LRMS [M+H] = 372.2

Example 63

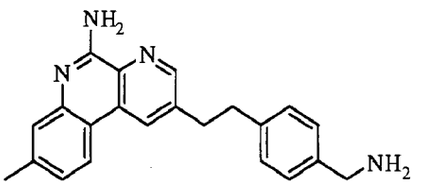
4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-2-methylbutan-2-ol



[000614] To a solution of methyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoate (from Example 61) in THF (0.2 M) at 0 °C was added in a dropwise fashion a solution of methylmagnesium bromide in THF (1.0 M, 2 eq). After stirring at room temperature overnight the reaction mixture was concentrated under vacuum and the resulting crude residue was purified by chromatography (silica gel, 50 – 100% EtOAc in hexanes) to afford 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-2-methylbutan-2-ol. ^{1}H NMR ($CDCl_3$): δ 8.64 (d, 1H), 8.34 (d, 1H), 8.06 (t, 1H), 7.57 (d, 1H), 7.30 – 7.20 (m, 2H), 7.18 – 7.07 (m, 4H), 6.67 (bs, 2H), 3.24 – 3.16 (dd, 2H), 3.08 – 3.01 (dd, 2H), 2.73 – 2.66 (m, 2H), 2.53 (s, 3H), 1.82 – 1.75 (m, 2H), 1.31 (s, 3H), 1.29 (s, 3H). LRMS [M+H] = 400.2

Example 64

2-(4-(aminomethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



Step 1: 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzonitrile

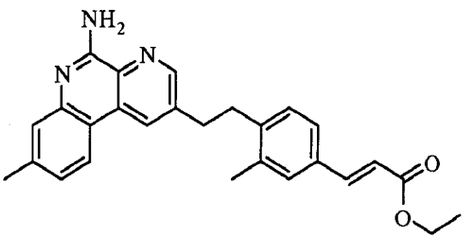
[000615] 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzonitrile was prepared from 4-ethynylbenzonitrile (commercially available) following the procedures described for Example 44 / Steps 3 to 5.

Step 2: 2-(4-(aminomethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000616] To a solution of 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzonitrile (from the previous step) in ethanol and ammonium hydroxide (4:1, 0.2 M) stirred at room temperature was added raney nickel (10 eq). The reaction mixture was stirred under hydrogen atmosphere until the conversion was complete as shown by TLC. The reaction mixture was filtered through a short celite pad. The celite pad was washed with EtOAc. Combined organic extracts were concentrated under vacuum and the resulting crude residue was purified by chromatography (silica gel, 50 – 100% EtOAc in hexanes) to afford product 2-(4-(aminomethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine. ^{1}H NMR **of the TFA salt**: (methanol-d_4): δ 8.81 (d, 1H), 8.79 (d, 1H), 8.38 (d, 1H), 7.51 (s, 1H), 7.44 (dd, 1H), 7.36 (dd, 4H), 4.07 (s, 2H), 3.29 (s, 2H), 3.20 – 3.14 (dd, 2H), 2.55 (s, 3H). LRMS [M+H] = 343.2

Example 65

(E)-ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylate



Step 1: (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)methanol

[000617] (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)methanol was prepared from methyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate (Example 115) following the procedures described for Example 42 / Step 3.

Step 2: 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzaldehyde

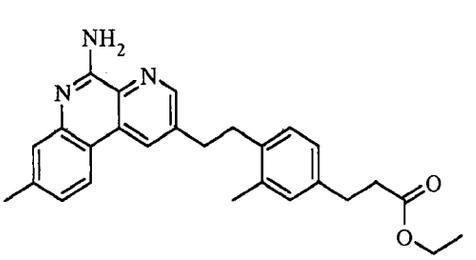
[000618] To a solution of (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)methanol (from the previous step) in DMSO was added 2-iodoxybenzoic acid (IBX, 2.5 eq). The reaction was stirred at room temperature for 3 hours before being diluted with water. Extraction with EtOAc followed by concentration gave a crude residue which was purified by chromatography (silica gel, 50 – 100% EtOAc in hexanes) to afford 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzaldehyde.

Step 3: (E)-ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylate

[000619] To a suspension of NaH (3 eq) in THF (0.2 M) stirred at 0 °C was added ethyl 2-(diethoxyphosphoryl)acetate (commercially available) (3 eq). After stirring for 30 minutes, a solution of 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzaldehyde (from the previous step) in THF (0.2 M) was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with sat. NH4Cl solution, and was extracted with EtOAc. Combined organic extracts were dried and concentrated to give a crude residue which was purified by chromatography (silica gel, 50 – 100% EtOAc in hexanes) to afford (E)-ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylate as a white solid. ^{1}H NMR: ($CDCl_3$): δ 8.54 (d, 1H), 8.29 (d, 1H), 7.99 (d, 1H), 7.57 (d, 1H), 7.44 (s, 1H), 7.23 (dd, 1H), 7.11 (dd, 1H), 7.05 (d, 1H), 6.33 (d, 1H), 5.93 (s, 2H), 4.19 (q, 2H), 3.10 – 2.95 (m, 4H), 2.44 (s, 3H), 2.23 (s, 3H), 1.26 (t, 3H). LRMS [M+H] = 426.2

Example 66

ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoate

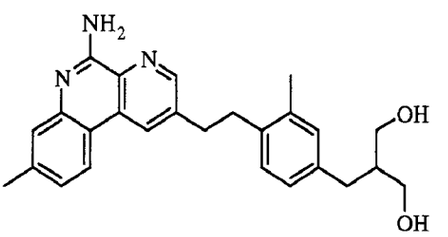


[000620] Ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoate was prepared from (E)-ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylate (from Example 65) following the procedures described for Example 44 / Step 5. ^{1}H NMR: ($CDCl_3$): δ 8.55 (d, 1H),

8.26 (d, 1H), 7.99 (d, 1H), 7.45 (s, 1H), 7.12 (dd, 1H), 6.98 -6.88 (m, 3H), 6.02 (s, 2H), 4.06 (q, 2H), 3.04 (dd, 2H), 2.93 (dd, 2H), 2.83 (t, 2H), 2.53 (t, 2H), 2.44 (s, 3H), 2.19 (s, 3H), 1.17 (t, 3H). LRMS [M+H] = 428.2

Example 67

2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzyl)propane-1,3-diol



Step 1: diethyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzyl)malonate

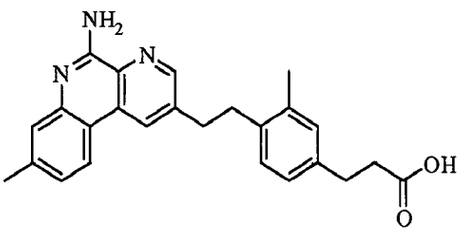
[000621] To a stirred solution of (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)methanol (from Example 65 / Step 1) (0.2 M) and diethyl malonate (2 eq) in dry toluene was added tributylphosphine (2 eq) and N^1,N^1,N^2,N^2-tetramethyldiazene-1,2-dicarboxamide (2 eq). The reaction mixture was stirred at 120 °C overnight. Upon completion of the reaction, the reaction mixture was concentrated under vacuum and the resulting crude residue was purified by chromatography (silica gel, 50 - 100% EtOAc in hexanes) to afford diethyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzyl)malonate as a white solid.

Step 2: 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzyl)propane-1,3-diol

[000622] 2-(4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzyl)propane-1,3-diol was prepared from diethyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzyl)malonate (from the previous step) following the procedures described for Example 42 / Step 3. ^{1}H NMR: (methanol- d_4): δ 8.51 (d, 1H), 8.39 (d, 1H), 8.05 (d, 1H), 7.45 (s, 1H), 7.10 (dd, 1H), 6.91 -6.87 (m, 2H), 6.83 (dd, 1H), 3.42 (d, 4H), 3.08 – 3.02 (m, 2H), 2.96 – 2.91 (m, 2H), 2.47 (d, 2H), 2.38 (s, 3H), 2.13 (s, 3H). LRMS [M+H] = 416.2

Example 68

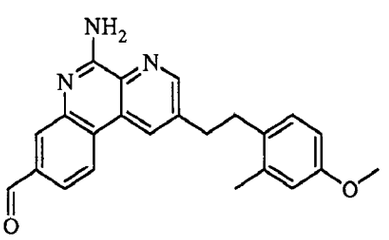
3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoic acid



[000623] A solution of ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoate (from Example 66) in 1 N NaOH, THF and methanol (1:5:2, 0.1 N) was heated at 60 °C for 3 hours. After cooling to room temperature the reaction mixture was neutralized with 1 N HCl to pH 7, and was concentrated to give a crude residue which was purified by chromatography (silica gel, 0 – 20% methanol in dichloromethane) to afford (E)-ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylate as a white solid. ^{1}H NMR: (methanol- d_4): δ 8.73 (d, 1H), 8.54 (d, 1H), 8.20 (d, 1H), 7.45 (s, 1H), 7.37 (d, 1H), 7.00 -6.97 (m, 2H), 6.92 (d, 1H), 3.19 (t, 2H), 3.04 (t, 2H), 2.81 (t, 2H), 2.53 (t, 2H), 2.50 (s, 3H), 2.25 (s, 3H). LRMS [M+H] = 400.2

Example 69

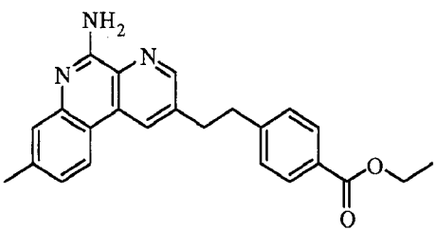
5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridine-8-carbaldehyde



[000624] 5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridine-8-carbaldehyde was prepared from (5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol (from Example 108) following the procedures described for Example 65 / Step 2. ^{1}H NMR: ($CDCl_3$): δ 10.19 (s, 1H), 8.74 (d, 1H), 8.43 (d, 1H), 8.32 (d, 1H), 8.18 (d, 1H), 7.88 (dd, 1H), 7.00 (d, 1H), 6.76 (d, 1H), 6.70 (dd, 1H), 6.30 (s, 2H), 3.80 (s, 3H), 3.16 (dd, 2H), 3.02 (dd, 2H), 2.29 (s, 3H). LRMS [M+H] = 372.2

Example 70

ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoate



Step 1: ethyl 4-((5-chloro-6-cyanopyridin-3-yl)ethynyl)benzoate

[000625] A solution of 3,5-dichloropicolinonitrile (commercially available) (1.0 eq.), ethyl 4-ethynylbenzoate (commercially available) (1.0 eq.), trans-dichlororbis(triphenylphosphine)palladium (II) (10 mol%), copper (I) iodide (20 mol%), and triethylamine (5.0 eq.) in DMF (0.3 M) was stirred at 50°C for 3 hours. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and 10% aqueous ammonium hydroxide. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-20% ethyl acetate in hexane to give ethyl 4-((5-chloro-6-cyanopyridin-3-yl)ethynyl)benzoate as a white solid .

Step 2: ethyl 4-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)benzoate

[000626] A solution of ethyl 4-((5-chloro-6-cyanopyridin-3-yl)ethynyl)benzoate (from the previous step) (1.0 eq.), tert-butyl 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from Example 5 / Step 2) (2.6 eq.), tetrakis(triphenylphosphine)palladium (10 mol%), and potassium carbonate (5.3 eq.) in toluene/ethanol (2:1, 0.2 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction mixture was diluted with 2% MeOH in DCM. The two phases were separated. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-40% ethyl acetate in toluene to give ethyl 4-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)benzoate.

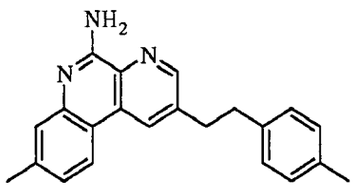
Step 3: ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoate

[000627] A solution of ethyl 4-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)benzoate (from the previous step) (1.0 eq.) in THF/ethyl acetate (1:1, 0.05M) was flushed with nitrogen and palladium on carbon (10 wt%) was added. The reaction vessel was evacuated, flushed with hydrogen, and stirred overnight at room temperature. The reaction mixture was filtered through celite, washed with 2% MeOH in DCM, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% MeOH in DCM

to give ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoate. ^{1}H NMR (Acetone- d_6): δ 8.80 (s, 1H), 8.69 (s, 1H), 8.25 (d, 1H), 7.90 (d, 2H), 7.40-7.42 (m, 3H), 7.12 (d, 1H), 6.55 (br, 2H), 4.28 (q, 2H), 3.2-3.3 (m, 4H), 2.44 (s, 3H), 1.31 (t, 3H). LRMS [M+H] = 386.2

Example 71

8-methyl-2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine



Step 1: 3-chloro-5-(p-tolylethynyl)picolinonitrile

[000628] A solution of 3,5-dichloropicolinonitrile (commercially available) (1.0 eq.), 1-ethynyl-4-methylbenzene (commercially available) (1.0 eq.), trans-dichlororbis(triphenylphosphine)palladium (II) (10 mol%), copper (I) iodide (20 mol%), and triethylamine (5.0 eq.) in DMF (0.3 M) was stirred at 50°C for 3 hours. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and 10% aqueous ammonium hydroxide. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by stirring in hot ether/hexane mixtures and filtered to give 3-chloro-5-(p-tolylethynyl)picolinonitrile.

Step 2: 8-methyl-2-(p-tolylethynyl)benzo[f][1,7]naphthyridin-5-amine

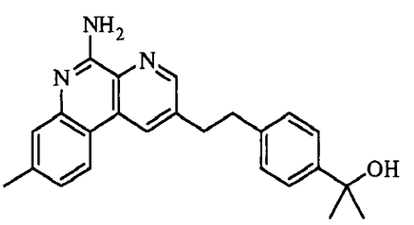
[000629] A solution of 3-chloro-5-(p-tolylethynyl)picolinonitrile (from the previous step) (1.0 eq.), tert-butyl 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from Example 5 / Step 2) (1.2 eq.), tetrakis(triphenylphosphine)palladium (10 mol%), and 2N sodium carbonate aqueous solution (4.0 eq.) in toluene/ethanol (2:1, 0.2 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction mixture was diluted with 2% MeOH in DCM. The two phases were separated, and the aqueous layer was extracted with 2% MeOH in DCM twice. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-40% ethyl acetate in toluene to give 8-methyl-2-(p-tolylethynyl)benzo[f][1,7]naphthyridin-5-amine.

Step 3: 8-methyl-2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine

[000630] A solution of 8-methyl-2-(p-tolylethynyl)benzo[f][1,7]naphthyridin-5-amine (from the previous step) (1.0 eq.) in EtOH/ethyl acetate (1:1, 0.05M) was flushed with nitrogen and palladium on carbon (10 wt%) was added. The reaction vessel was evacuated, flushed with hydrogen, and stirred overnight at room temperature. The reaction mixture was filtered through celite, washed with 2% MeOH in DCM, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% MeOH in DCM to give 8-methyl-2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine. ^{1}H NMR (Acetone- d_6): δ 8.74 (s, 1H), 8.68 (s, 1H), 8.24 (d, 1H), 7.41 (s, 1H), 7.13-7.15 (m, 3H), 7.06 (d, 2H), 6.6 (br, 2H), 3.19 (t, 2H), 3.06 (t, 2H), 2.44 (s, 3H), 2.25 (s, 3H). LRMS [M+H] = 328.1

Example 72

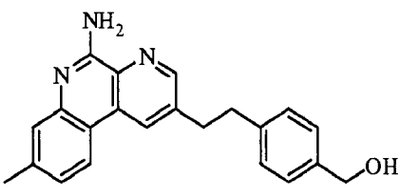
2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-2-ol



[000631] To a solution of ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoate (from Example 70) (1.0 eq.) in DCM at 0°C was added 3.0 M methyl magnesium iodide (10eq.) in ether and warmed to room temperature overnight. The reaction was cooled to 0°C and quenched with 1N HCl aqueous solution and ether. After stirring for 15 minutes, the reaction mixture was neutralized with saturated aqueous sodium bicarbonate solution. The two phases were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by RP-HPLC using a 10-50% MeCN in water gradient followed by extraction in DCM to give 2-(4-(2-(5-amino-8 methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-2-ol. ^{1}H NMR (Acetone- d_6): δ 8.73 (m, 2H), 8.22 (d, 1H), 7.40-7.44 (m, 3H), 7.20 (d, 2H), 7.12 (d, 1H), 6.5 (br, 2H), 3.94 (s, 1H), 3.21 (t, 2H), 3.08 (t, 2H), 2.44 (s, 3H), 1.47 (s, 6H). LRMS [M+H] = 372.2

Example 73

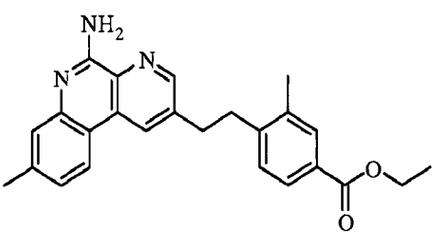
(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol



[000632] To a solution of ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoate (Example 70) (1.0 eq.) in THF (0.1 M) at 0°C was added 1.0 M lithium triethylborohydride in THF (10 eq.) and warmed to room temperature over 2 hours. 1N HCl aqueous solution was added slowly to quench the reaction, and the mixture was heated to reflux for 30 minutes. The reaction mixture was neutralized with saturated aqueous sodium bicarbonate solution. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (EA). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by RP-HPLC using a 10-50% MeCN in water gradient followed by extraction in DCM to give (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol. ^{1}H NMR (Acetone- d_6): δ 8.77 (s, 1H), 8.69 (s, 1H), 8.26 (d, 1H), 7.40 (s, 1H), 7.21-7.28 (m, 4H), 7.13 (d, 1H), 6.5 (br, 2H), 4.56 (s, 2H), 4.1 (br t, 1H), 3.10-3.23 (m, 4H), 2.44 (s, 3H). LRMS [M+H] = 344.2

Example 74

ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate



Step 1: ethyl 4-bromo-3-methylbenzoate

[000633] To a solution of 4-bromo-3-methylbenzoic acid (commercially available) (1.0 eq.) in EtOH (0.3 M) was added thionyl chloride (1.5 eq.) and heated to reflux for 2 hours. The solvent was concentrated *en vaccuo*, and the residue was diluted in ether and neutralized with saturated aqueous sodium bicarbonate solution. The two phases were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated en vaccuo to give ethyl 4-bromo-3-methylbenzoate.

Step 2: ethyl 3-methyl-4-((triethylsilyl)ethynyl)benzoate

[000634] A solution of ethyl 4-bromo-3-methylbenzoate (from the previous step) (1.0 eq.), triethyl(ethynyl)silane (1.1 eq.), trans-dichlororbis(triphenylphosphine)palladium (II) (10 mol%),

copper (I) iodide (20 mol%), and triethylamine (5.0 eq.) in DMF (0.3 M) was stirred at 60°C overnight. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and 10% aqueous ammonium hydroxide. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% ethyl acetate in hexane to give ethyl 3-methyl-4-((triethylsilyl)ethynyl)benzoate as a yellow oil.

Step 3: ethyl 4-ethynyl-3-methylbenzoate

[000635] To a solution of ethyl 3-methyl-4-((triethylsilyl)ethynyl)benzoate (from the previous step) (1.0 eq.) in THF (0.3 M) at 0°C was added dropwise 1.0 M TBAF in THF (1.2 eq.). After stirring for 10 minutes at 0°C, the reaction was quenched with saturated aqueous sodium bicarbonate solution. The two phases were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% ethyl acetate in hexane to give ethyl 4-ethynyl-3-methylbenzoate as a white solid.

Step 4: ethyl 4-((5-chloro-6-cyanopyridin-3-yl)ethynyl)-3-methylbenzoate

[000636] A solution of 3,5-dichloropicolinonitrile (1.0 eq.), ethyl 4-ethynyl-3-methylbenzoate (from the previous step) (1.0 eq.), trans-dichlororbis(triphenylphosphine)palladium (II) (10 mol%), copper (I) iodide (20 mol%), and triethylamine (5.0 eq.) in DMF (0.3 M) was stirred at 50°C for 3 hours. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and 10% aqueous ammonium hydroxide. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-10% ethyl acetate in hexane to give ethyl 4-((5-chloro-6-cyanopyridin-3-yl)ethynyl)-3-methylbenzoate as a white solid.

Step 5: ethyl 4-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)-3-methylbenzoate

[000637] A solution of ethyl 4-((5-chloro-6-cyanopyridin-3-yl)ethynyl)-3-methylbenzoate (from the previous step) (1.0 eq.), tert-butyl 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from Example 5 / Step 2) (1.1 eq.), tetrakis(triphenylphosphine)palladium (8 mol%), and potassium carbonate (3.0 eq.) in toluene/ethanol (9:1, 0.2 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction mixture was diluted with 2% MeOH in DCM. The two phases were separated. The combined organic layers were washed with brine,

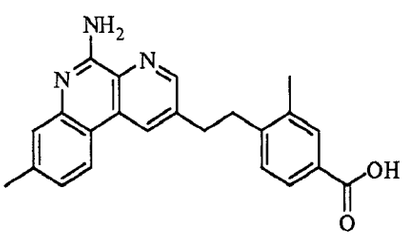
dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-40% ethyl acetate in toluene to give ethyl 4-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)-3-methylbenzoate.

Step 6: ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate

[000638] A solution of ethyl 4-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)-3-methylbenzoate (from the previous step) (1.0 eq.) in THF/ethyl acetate (1:1, 0.05M) was flushed with nitrogen and added 10% palladium on carbon (10 wt%). The reaction vessel was evacuated, flushed with hydrogen, and stirred overnight at room temperature. The reaction mixture was filtered through celite, washed with 2% MeOH in DCM, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 30-100% EA in hexane to give ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate. ^{1}H NMR (Acetone- d_6): δ 8.79 (s, 1H), 8.71 (s, 1H), 8.24 (d, 1H), 7.80 (s, 1H), 7.73 (d, 1H), 7.40 (s, 1H), 7.31 (d, 1H), 7.12 (d, 1H), 6.5 (br, 2H), 4.29 (q, 2H), 3.19-3.22 (m, 4H), 2.44 (s, 3H), 2.39 (s, 3H), 1.31 (t, 3H). LRMS [M+H] = 400.2

Example 75

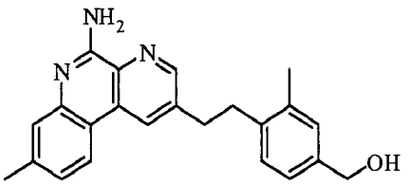
4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoic acid



[000639] To a solution of ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate (from Example 74) (1.0 eq.) in EtOH was added 1N aqueous sodium hydroxide (1.5 eq.) and heated to 80°C for 5 hours. The reaction mixture was neutralized by adding 1N aqueous HCl (1.5 eq.) and concentrated *en vaccuo*. The crude material was purified by RP-HPLC using a 10-50% MeCN in water gradient followed by concentration *en vaccuo* to give the TFA salt. ^{1}H NMR (DMSO- d_6) **of the TFA salt**: δ 7.94-7.96 (m, 2H), 7.55 (d, 1H), 7.00 (s, 1H), 6.91 (d, 1H), 6.62-6.66 (m, 2H), 6.39 (d, 1H), 2.36-2.5 (m, 4H), 1.73 (s, 3H), 1.54 (s, 3H). LRMS [M+H] = 372.2

Example 76

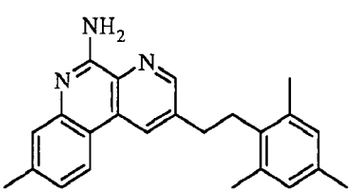
(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)methanol



[000640] To a solution of ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate (from Example 74) (1.0 eq.) in THF (0.1M) at -78°C was added 1.0 M DIBAL-H in toluene (10 eq.) and warmed to room temperature over 2 hours. 1.5 M Rochelle salt aqueous solution was added slowly to quench the reaction followed by addition of EA, and the mixture was stirred for 45 minutes. The two phases were separated, and the aqueous layer was extracted twice with EA. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by RP-HPLC using a 10-50% MeCN in water gradient followed by extraction in DCM to give (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)methanol. ^{1}H NMR (Acetone- d_6): δ 8.77 (s, 1H), 8.71 (s, 1H), 8.25 (d, 1H), 7.41 (s, 1H), 7.10-7.15 (m, 4H), 6.5 (br, 2H), 4.54 (s, 2H), 4.05 (br, 1H), 3.08-3.18 (m, 4H), 2.44 (s, 3H), 2.31 (s, 3H). LRMS [M+H] = 358.2

Example 77

8-methyl-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine



Step 1: 3-chloro-5-(mesitylethynyl)picolinonitrile

[000641] A solution of 3,5-dichloropicolinonitrile (1.0 eq.), 2-ethynyl-1,3,5-trimethylbenzene (commercially available) (1.0 eq.), trans-dichlororbis(triphenylphosphine)palladium (II) (10 mol%), copper (I) iodide (20 mol%), and triethylamine (5.0 eq.) in DMF (0.3 M) was stirred at 50°C for 3 hours. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and 10% aqueous ammonium hydroxide. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-10% ethyl acetate in hexane to give *3-chloro-5-(mesitylethynyl)picolinonitrile* a as white solid.

Step 2: 2-(mesitylethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

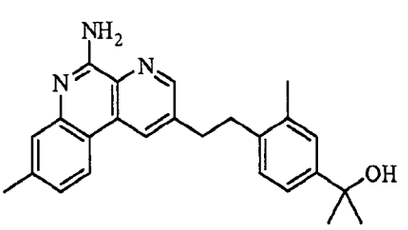
[000642] A solution of 3-chloro-5-(mesitylethynyl)picolinonitrile (from the previous step) (1.0 eq.), tert-butyl 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from Example 5 / Step 2) (1.1 eq.), tetrakis(triphenylphosphine)palladium (8 mol%), and 2N aqueous sodium carbonate solution (3.0 eq.) in toluene/ethanol (4:1, 0.2 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction mixture was diluted with 2% MeOH in DCM. The two phases were separated. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-40% ethyl acetate in toluene to give 2-(mesitylethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine.

Step 3: 8-methyl-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine

[000643] A solution of 2-(mesitylethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine (from the previous step) (1.0 eq.) in EtOH (0.05M) was flushed with nitrogen and added palladium on carbon (10 wt%). The reaction vessel was evacuated, flushed with hydrogen, and stirred overnight at rt. The reaction mixture was filtered through celite, washed with 2% MeOH in DCM, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-50% ethyl acetate in hexane to give 8-methyl-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine. ^1H NMR (Acetone- d_6): δ 8.73-8.74 (m, 2H), 8.25 (d, 1H), 7.42 (s, 1H), 7.14 (d, 1H), 6.83 (s, 2H), 6.55 (br, 2H), 3.07 (m, 4H), 2.47 (s, 3H), 2.29 (s, 6H), 2.22 (s, 3H). LRMS [M+H] = 356.2

Example 78

2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol

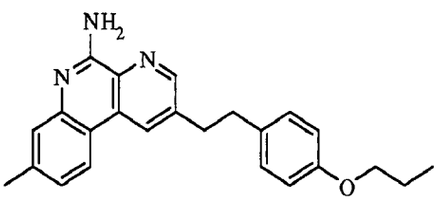


[000644] To a solution of ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate (from Example 74) (1.0 eq.) in DCM at 0°C was added 3.0 M methyl magnesium iodide (10eq.) in ether and warmed to room temperature overnight. The reaction was cooled to 0°C and quenched with water. After stirring for 15min, the reaction mixture was neutralized with saturated aqueous sodium bicarbonate solution and added EA. The two phases were separated, and the aqueous layer was extracted three times with EA. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was

purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% MeOH in DCM to give a 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol. ^{1}H NMR (Acetone- d_6): δ 8.72-8.75 (m, 2H), 8.23 (d, 1H), 7.41 (s, 1H), 7.32 (s, 1H), 7.25 (d, 1H), 7.12-7.14 (m, 2H), 6.6 (br, 2H), 3.91 (s, 1H), 3.07-3.18 (m, 4H), 2.44 (s, 3H), 2.31 (s, 3H), 1.48 (s, 6H). LRMS [M+H] = 386.2

Example 79

8-methyl-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine



Step 1: 3-chloro-5-((4-propoxyphenyl)ethynyl)picolinonitrile

[000645] A solution of 3,5-dichloropicolinonitrile (1.0 eq.), 1-ethynyl-4-propoxybenzene (commercially available) (1.0 eq.), trans-dichlororbis(triphenylphosphine)palladium (II) (10 mol%), copper (I) iodide (20 mol%), and triethylamine (5.0 eq.) in DMF (0.3 M) was stirred at 50°C for 3 hours. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and 10% aqueous ammonium hydroxide. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-10% ethyl acetate in hexane to give 3-chloro-5-((4-propoxyphenyl)ethynyl)picolinonitrile as a white solid.

Step 2: 3-chloro-5-(4-propoxyphenethyl)picolinonitrile

[000646] A solution of 3-chloro-5-((4-propoxyphenyl)ethynyl)picolinonitrile (from the previous step) (1.0 eq.) in EtOH (0.05M) was flushed with nitrogen and added platinum (VI) oxide (0.5 eq.). The reaction vessel was evacuated, flushed with hydrogen, and stirred for 5 hours at room temperature. The reaction mixture was filtered through celite, washed with 2% MeOH in DCM, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-15% ethyl acetate in hexane to give 3-chloro-5-(4-propoxyphenethyl)picolinonitrile.

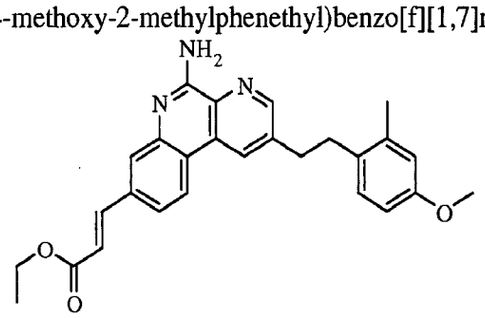
Step 3: 8-methyl-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine

[000647] A solution of 3-chloro-5-(4-propoxyphenethyl)picolinonitrile (from the previous step) (1.0 eq.), tert-butyl 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate

(from Example 5 / Step 2) (1.1 eq.), tetrakis(triphenylphosphine)palladium (8 mol%), and 2N aqueous sodium carbonate solution (3.0 eq.) in toluene (0.2 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction mixture was diluted with 2% MeOH in DCM. The two phases were separated. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-40% ethyl acetate in toluene to give 8-methyl-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine. ^{1}H NMR (Acetone-d_6): δ 8.74 (s, 1H), 8.67 (s, 1H), 8.24 (d, 1H), 7.41 (s, 1H), 7.15-7.17 (m, 3H), 6.81 (d, 2H), 6.5 (br, 2H), 3.87 (t, 2H), 3.18 (t, 2H), 3.04 (t, 2H), 2.44 (s, 3H), 1.73 (m, 2H), 0.99 (t, 3H). LRMS [M+H] = 372.2

Example 80

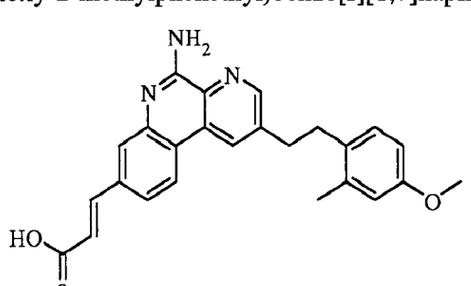
(E)-ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylate



[000648] (E)-ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylate was prepared from 5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridine-8-carbaldehyde (from Example 69) and ethyl 2-(diethoxyphosphoryl)acetate (commercially available) following the procedures described for Example 65 / Step 3. LRMS [M+H] = 442.2

Example 81

(E)-3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylic acid

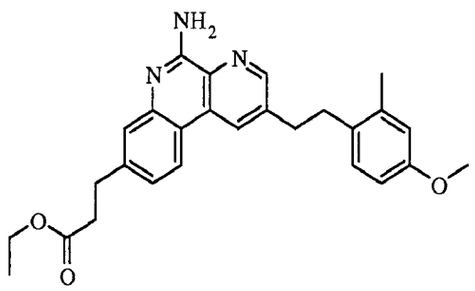


[000649] (E)-3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylic acid was prepared from (E)-ethyl 3-(5-amino-2-(4-methoxy-2-

methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylate (from Example 80) following the procedures described for Example 68. ^{1}H NMR of **TFA salt** (DMSO- d_6): δ 12.66 (s, 1H), 9.09 (s, 1H), 8.88 (s, 1H), 8.66 (d, 1H), 7.95 (d, 1H), 7.91 (s, 1H), 7.75 (d, 1H), 7.10 (d, 1H), 6.77 – 6.71 (m, 2H), 6.68 (dd, 1H), 3.70 (s, 3H), 3.16 (t, 2H), 3.00 (t, 2H), 2.30 (s, 3H). LRMS [M+H] = 414.2

Example 82

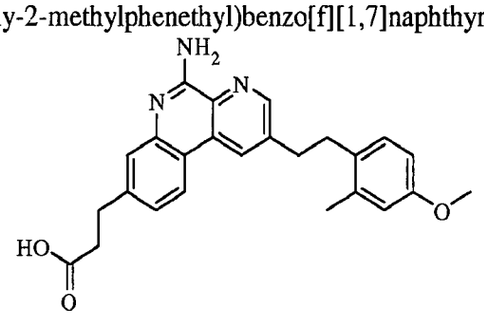
ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoate



[000650] Ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoate was prepared from (E)-ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylate (from Example 80) following the procedures described for Example 44 / Step 5. ^{1}H NMR ($CDCl_3$): δ 8.63 (d, 1H), 8.37 (d, 1H), 8.13 (d, 1H), 7.56 (d, 1H), 7.24 (dd, 1H), 7.02 (d, 1H), 6.75 (d, 1H), 6.69 (dd, 1H), 6.15 (br s, 2H), 4.17 (q, 2H), 3.79 (s, 3H), 3.12 (dd, 4H), 2.99 (dd, 2H), 2.75 (t, 2H), 2.29 (s, 3H), 1.27 (t, 2H), 0.99 (t, 3H). LRMS [M+H] = 444.2

Example 83

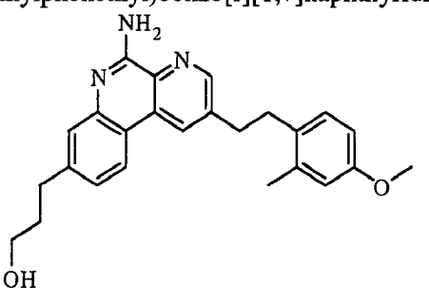
3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoic acid



[000651] 3-(5-Amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoic acid was prepared from ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoate (from Example 82) following the procedures described for Example 68. ^{1}H NMR (DMSO- d_6): δ 12.18 (s, 1H), 8.84 (d, 1H), 8.70 (d, 1H), 8.36 (d, 1H), 7.39 (d, 1H), 7.20 (dd, 1H), 7.09 (m, 2H), 6.74 (d, 1H), 6.68 (dd, 1H), 3.70 (s, 3H), 3.09 (dd, 2H), 2.96 (dd, 4H), 2.63 (t, 2H), 2.27 (s, 3H). LRMS [M+H] = 416.2

Example 84

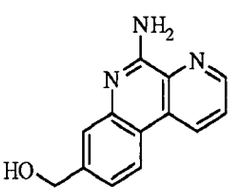
3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propan-1-ol



[000652] 3-(5-Amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propan-1-ol was prepared from ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoate (from Example 82) following the procedures described for Example 42 / Step 3. ^{1}H NMR ($CDCl_3$): δ 8.54 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.48 (d, 1H), 7.15 (dd, 1H), 6.93 (d, 1H), 6.66 (d, 1H), 6.61 (dd, 1H), 5.98 (br s, 2H), 3.71 (s, 3H), 3.66 (t, 2H), 3.03 (dd, 2H), 2.91 (dd, 2H), 2.81 (t, 2H), 2.20 (s, 3H), 1.98 – 1.90 (m, 2H). LRMS [M+H] = 402.2

Example 85

(5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol



Step 1: 2-(tert-butoxycarbonylamino)-4-(methoxycarbonyl)phenylboronic acid

[000653] A solution of 2-amino-4-(methoxycarbonyl)phenylboronic acid hydrochloride (commercially available) (1.0 eq.), triethylamine (3.0 eq.), di-*tert*-butyl dicarbonate (1.1 eq.), and DMAP (0.1 eq.) in CH_3CN (0.3 M) was stirred at 40°C overnight. After cooling to ambient temperature, the reaction mixture was concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-30% MeOH/DCM to give 2-(tert-butoxycarbonylamino)-4-(methoxycarbonyl)phenylboronic acid as a brown solid.

Step 2: methyl 5-aminobenzo[f][1,7]naphthyridine-8-carboxylate

[000654] A solution of 2-(*tert*-butoxycarbonylamino)-4-(methoxycarbonyl) phenylboronic acid (from the previous step) (1.0 eq.) and 3-bromopicolinonitrile (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (2.0 eq.) in toluene/ethanol (2:1, 0.03 M) was stirred at 100°C overnight. After cooling to ambient

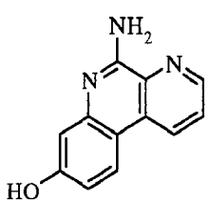
temperature, the reaction mixture was filtered to collect the precipitate. The precipitate was rinsed with EtOAc to give methyl 5-aminobenzo[f][1,7]naphthyridine-8-carboxylate as a pale brown solid.

Step 3: (5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol

[000655] To a solution of methyl 5-aminobenzo[f][1,7]naphthyridine-8-carboxylate (from the previous step) (1.0 eq.) in EtOH (0.03M) was added $NaBH_4$ (10 eq.) at 25°C. The solution was heated to 80°C for 5 hours. After cooling to ambient temperature, the reaction mixture was concentrated *en vaccuo*. The residue was portionized between saturated $NaHCO_3$ and EtOAc. The layers were separated and aqueous layer was extracted with EtOAc twice. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-10% MeOH/DCM to give (5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol as an off white solid: ^{1}H NMR (methanol- d_4): δ 8.82 (dd, 1H), 8.77 (dd, 1H), 7.26 (d, 1H), 7.70 (dd, 1H), 7.50(d, 1H), 7.27 (dd, 1H), 4.66 (s, 2H). LRMS [M+H] = 226.1.

Example 86

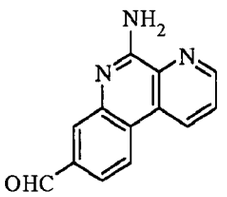
5-aminobenzo[f][1,7]naphthyridin-8-ol



[000656] To a solution of 8-methoxybenzo[f][1,7]naphthyridin-5-amine (from Example 10) (1.0 eq.) in DCM (0.04 M) was added BBr_3 (2.5 eq.) dropwise under N_2 at -20°C. The reaction was allowed to warm to ambient temperature over 30 minutes. The reaction was then stirred overnight. The reaction was quenched with saturated $NaHCO_3$ and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-20% MeOH/DCM to give 5-aminobenzo[f][1,7]naphthyridin-8-ol as a yellow solid: ^{1}H NMR (acetone- d_6): δ 8.90 (dd, 1H), 8.83 (dd, 1H), 8.32 (d, 1H), 7.83 (dd, 1H), 7.11 (br s, 2H), 7.10(d, 1H), 6.96 (dd, 1H), 5.86 (br s, 1H). LRMS [M+H] = 212.1.

Example 87

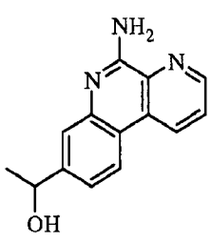
5-aminobenzo[f][1,7]naphthyridine-8-carbaldehyde



[000657] A solution of (5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol (from Example 85) (1.0 eq.) and activated MnO_2 (20 eq.) in DCM (0.1 M) was stirred at ambient temperature over night. The reaction mixture was diluted with DCM. The MnO_2 was filtered off, and the filtrate was concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-10% MeOH/DCM to give 5-aminobenzo[f][1,7]naphthyridine-8-carbaldehyde as a yellow solid: ^{1}H NMR (acetone- d_6): δ 10.19 (s, 1H), 9.14 (dd, 1H), 9.01 (dd, 1H), 8.63 (d, 1H), 8.14 (d, 1H), 7.93(dd, 1H), 7.81 (dd, 1H), 6.96 (br s, 2H). LRMS [M+H] = 224.1

Example 88

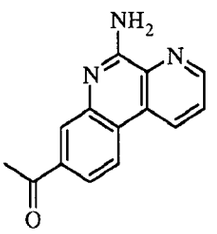
1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanol



[000658] To a solution of 5-aminobenzo[f][1,7]naphthyridine-8-carbaldehyde (from Example 87) (1.0 eq.) in THF (0.02M) was added MeLi (2.5 eq.) at -78°C. The reaction was allowed to warm to ambient temperature overnight. The reaction was quenched by saturated NH_4Cl and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% MeOH/DCM to give 1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanol as a yellow solid: ^{1}H NMR (methanol- d_4): δ 8.94 (dd, 1H), 8.88 (dd, 1H), 8.38 (d, 1H), 7.81 (dd, 1H), 7.62(d, 1H), 7.41 (dd, 1H), 4.97 (q, 1H), 1.53 (d, 3H). LRMS [M+H] = 240.1.

Example 89

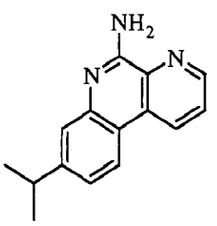
1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanone



[000659] A solution 1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanol (from Example 88) (1.0 eq.) and activated MnO_2 (20 eq.) in DCM (0.1 M) was stirred at ambient temperature over night. The reaction mixture was diluted with DCM. The MnO_2 was filtered off, and the filtrate was concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% MeOH/DCM to give 1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanone as a yellow solid: ^{1}H NMR (acetone- d_6): δ 9.11(dd, 1H), 8.99 (dd, 1H), 8.56 (d, 1H), 8.20 (d, 1H), 7.94-7.88(m, 2H), 6.90 (br s, 2H), 2.70 (s, 3H). LRMS [M+H] = 238.1.

Example 90

8-isopropylbenzo[f][1,7]naphthyridin-5-amine



Step 1: 2-(5-aminobenzo[f][1,7]naphthyridin-8-yl)propan-2-ol

[000660] To a solution of methyl 5-aminobenzo[f][1,7]naphthyridine-8-carboxylate (from Example 85 / Step 2) (1.0 eq.) in THF (0.02M) was added MeLi (10 eq.) at -78°C. The reaction was allowed to warm to ambient temperature overnight. The reaction was quenched by saturated NH_4Cl and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-10% MeOH/DCM to give 2-(5-aminobenzo[f][1,7]naphthyridin-8-yl)propan-2-ol as a yellow oil.

Step 2: 8-(prop-1-en-2-yl)benzo[f][1,7]naphthyridin-5-amine

[000661] A solution of 2-(5-aminobenzo[f][1,7]naphthyridin-8-yl)propan-2-ol (from the previous step) (1.0 eq.) and *p*-TsOH (2 eq.) in toluene (0.01 M) was stirred at 90°C for 6 hours. The reaction was quenched by saturated $NaHCO_3$ and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *en vaccuo* to obtain a crude

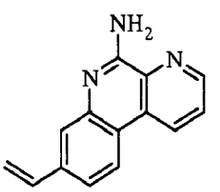
residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% MeOH/DCM to give 8-(prop-1-en-2-yl)benzo[f][1,7]naphthyridin-5-amine as a yellow solid.

Step 3: 8-isopropylbenzo[f][1,7]naphthyridin-5-amine

[000662] A mixture of 8-(prop-1-en-2-yl)benzo[f][1,7]naphthyridin-5-amine (from the previous step) (1.0 eq) and Pd/C (wet, 10% wt) in EtOH was stirred under H_2 balloon overnight. The reaction mixture was diluted with DCM. The Pd/C was filtered off through celite, and the filtrate was concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-60% EtOAc/Hexanes to give 8-isopropylbenzo[f][1,7]naphthyridin-5-amine as a yellow solid: ^{1}H NMR (acetone- d_6): δ 8.98(dd, 1H), 8.88 (dd, 1H), 8.37 (d, 1H), 7.83 (dd, 1H), 7.49 (d, 1H), 7.27(dd, 1H), 6.66 (br s, 2H), 3.10-3.00 (m, 1H), 1.33 (d, 6H). LRMS [M+H] = 238.1.

Example 91

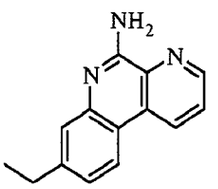
8-vinylbenzo[f][1,7]naphthyridin-5-amine



[000663] To a solution of methyl triphenyl phosphonium iodide (6.0 eq.) was added *n*BuLi (7.0 eq.) at -78°C. The reaction mixture was allowed to warm to 0°C and stirred for 30 minutes (deep orange color). The reaction was again cooled down to -78°C and 5-aminobenzo[f][1,7]naphthyridine-8-carbaldehyde (from Example 87) (1.0 eq.) in THF was introduced dropwised to the reaction. The reaction was allowed to warm to ambient temperature overnight. The reaction was quenched by saturated NH_4Cl and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-50% EtOAc/Hexanes to give 8-vinylbenzo[f][1,7]naphthyridin-5-amine as a white solid: ^{1}H NMR (acetone- d_6): ^{1}H NMR (acetone- d_6): δ 9.00 (dd, 1H), 8.90 (dd, 1H), 8.41 (d, 1H), 7.84 (dd, 1H), 7.65 (d, 1H), 7.52(dd, 1H), 6.91 (dd, 1H), 6.77 (br s, 2H), 5.97 (dd, 1H), 5.34 (dd, 1H). LRMS [M+H] = 222.1.

Example 92

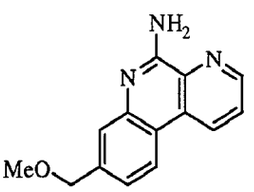
8-ethylbenzo[f][1,7]naphthyridin-5-amine



[000664] A mixture of 8-vinylbenzo[f][1,7]naphthyridin-5-amine (1.0 eq) (from Example 91) and Pd/C (wet, 10% wt) in EtOH was stirred under H_2 balloon overnight. The reaction mixture was diluted with DCM. The Pd/C was filtered off through celite, and the filtrate was concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-60% EtOAc/Hexanes to give 8-ethylbenzo[f][1,7]naphthyridin-5-amine as a white foam: ^{1}H NMR (acetone- d_6): δ 8.98(dd, 1H), 8.88 (dd, 1H), 8.35 (d, 1H), 7.82 (dd, 1H), 7.46 (d, 1H), 7.22(dd, 1H), 6.63 (br s, 2H), 2.78 (q, 2H), 1.30 (t, 3H). LRMS [M+H] = 224.1.

Example 93

8-(methoxymethyl)benzo[f][1,7]naphthyridin-5-amine



Step 1: tert-butyl 2-chloro-5-(methoxymethyl)phenylcarbamate

[000665] To a solution of 2-chloro-5-(methoxymethyl)aniline (commercially available) (1.0 eq.) in THF (0.2M) at 0°C under N_2 atmosphere was added dropwise 1M NaHMDS (2.5 eq.). The reaction was stirred for 15 minutes at 0°C, and a solution of di-*tert*-butyl dicarbonate in THF was added. The reaction was warmed to ambient temperature overnight. The solvent was evaporated, and the resulting residue was quenched with 0.1N HCl aqueous solution. The aqueous suspension was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated en vaccuo. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-30% EtOAc/Hexanes to give tert-butyl 2-chloro-5-(methoxymethyl)phenylcarbamate as a colorless oil.

Step 2: tert-butyl 5-(methoxymethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate

[000666] *Tert*-butyl 2-chloro-5-(methoxymethyl)phenylcarbamate (from the previous step) (1.0 eq.), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.0 eq.), Pd_2dba_3 (2.5%), XPhos (10%), and KOAc (3 eq.) were mixed in dioxane (0.2 M) under N_2 atmosphere. The reaction was

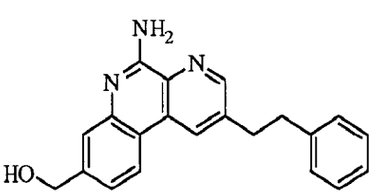
heated to 110°C and stirred overnight. The resulting suspension was cooled to ambient temperature, diluted with ether, filtered through celite, and the filtrate was concentrated *en vaccuo*. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-20% EtOAc/Hexanes to give tert-butyl 5-(methoxymethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate as a white foam.

Step 3: 8-(methoxymethyl)benzo[f][1,7]naphthyridin-5-amine

[000667] A solution of *tert*-butyl 5-(methoxymethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from the previous step) (1.0 eq.) and 3-bromopicolino-nitrile (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction mixture was diluted with 2% MeOH in DCM and water. The two phases were separated, and the aqueous layer was extracted twice with 2% MeOH in DCM. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-100% EtOAc/Hexanes to give 8-(methoxymethyl)benzo[f][1,7]naphthyridin-5-amine as a white solid: ^1H NMR (methanol- d_4): δ 8.97(dd, 1H), 8.91 (dd, 1H), 8.41 (dd, 1H), 7.83 (dd, 1H), 7.59 (d, 1H), 7.37(dd, 1H), 4.62 (s, 2H), 3.45 (s, 3H). LRMS [M+H] = 240.1.

Example 94

(5-amino-2-phenethylbenzo[f][1,7]naphthyridin-8-yl)methanol



Step 1: methyl 5-amino-2-phenethylbenzo[f][1,7]naphthyridine-8-carboxylate

[000668] A solution of 2-(*tert*-butoxycarbonylamino)-4-(methoxycarbonyl) phenylboronic acid (from Example 85 / Step1) (1.0 eq.) and 2-chloro-6-phenethylnicotinonitrile (prepared from *(E)*-3-chloro-5-styrylpicolinonitrile (from Example 32 / Step 1) following the procedure described in Example 114 / Step3) (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (2.0 eq.) in toluene/ethanol (2:1, 0.03 M) was stirred at 100°C

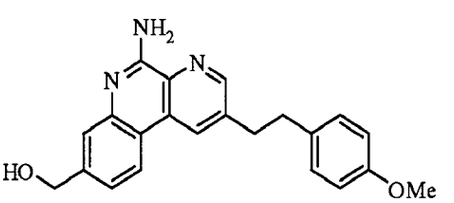
overnight. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and water. The two phases were separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-60% EtOAc/Hexanes to give methyl 5-amino-2-phenethylbenzo[f][1,7]naphthyridine-8-carboxylate as a white solid.

Step 2: (5-amino-2-phenethylbenzo[f][1,7]naphthyridin-8-yl)methanol

[000669] To a solution of methyl 5-amino-2-phenethylbenzo[f][1,7]naphthyridine-8-carboxylate (from the previous step) (1.0 eq.) in THF (0.03M) was added Super-H (10 eq.) at 0°C. The solution was allowed to warm to ambient temperature over 30 min. The reaction was quenched by water until no bubbling. The layers were separated and aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-10% MeOH/DCM to give (5-amino-2-phenethylbenzo[f][1,7]naphthyridin-8-yl)methanol as an off white solid: ^{1}H NMR (methanol- d_4): δ 8.63 (dd, 1H), 8.56 (dd, 1H), 8.24 (d, 1H), 7.57 (d, 1H), 7.35 (dd, 1H), 7.27-7.15 (m, 5H), 4.75 (s, 2H), 3.20 (t, 2H), 3.06 (t, 2H). LRMS [M+H] = 330.1.

Example 95

(5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol



Step 1: methyl 5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridine-8-carboxylate

[000670] A solution of 2-(*tert*-butoxycarbonylamino)-4-(methoxycarbonyl) phenylboronic acid (from Example 85 / Step1) (1.0 eq.) and 2-chloro-6-(4-methoxyphenethyl)nicotinonitrile (prepared from reaction of 3,5-dichloropicolinonitrile with 1-ethynyl-4-methoxybenzene following the procedure described in Example 44 / Step 3 and reduction of the product following the procedure described in Example 114 / Step3) (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (2.0 eq.) in toluene/ethanol (2:1, 0.03 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and water. The two phases were separated, and the aqueous layer was extracted twice with

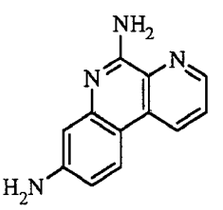
EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% EtOAc/Hexanes to give methyl 5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridine-8-carboxylate as a white solid.

Step 2: (5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol

[000671] To a solution of methyl 5-amino-2-(4-methoxyphenethyl)benzo[f][1,7] naphthyridine-8-carboxylate (from the previous step) (1.0 eq.) in THF (0.03M) was added Super-H (10 eq.) at 0°C. The solution was allowed to warm to ambient temperature over 30 minutes. The reaction was quenched by water until no bubbling. The layers were separated and aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-100% EtOAc/Hexanes to give (5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol as an off white solid (31%): ^{1}H NMR (acetone- d_6): δ 8.79 (d, 1H), 8.70 (d, 1H), 8.35 (d, 1H), 7.61 (d, 1H), 7.33 (dd, 1H), 7.13 (d, 2H), 6.83 (d, 2H), 6.62 (br s, 2H), 4.47 (s, 2H), 4.40 (br s, 1H), 3.75 (s, 3H), 3.22 (t, 2H), 3.06 (t, 2H). LRMS [M+H] = 360.2.

Example 96

benzo[f][1,7]naphthyridine-5,8-diamine



Step 1: tert-butyl 2-bromo-5-nitrophenylcarbamate

[000672] To a solution of 2-bromo-5-nitroaniline (commercially available) (1.0 eq.) in THF (0.2M) at 0°C under N_2 atmosphere was added dropwise 1M NaHMDS (2.5 eq.). The reaction was stirred for 15 minutes at 0°C, and a solution of di-*tert*-butyl dicarbonate in THF was added. The reaction was warmed to ambient temperature overnight. The solvent was evaporated, and the resulting residue was quenched with 0.1N HCl aqueous solution. The aqueous suspension was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-30% EtOAc/Hexanes to give tert-butyl 2-bromo-5-nitrophenylcarbamate as a colorless oil.

Step 2: tert-butyl 5-nitro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl carbamate

[000673] *Tert*-butyl 2-bromo-5-nitrophenylcarbamate (from the previous step) (1.0 eq.), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.8 eq.), dichloro[1,1'-bis(diphenyl phosphino)ferrocene]palladium (II) (5%), and sodium acetate (4.5 eq.) were mixed in dioxane (0.2 M) under N_2 atmosphere. The reaction was heated to 100°C and stirred overnight. The resulting suspension was cooled to ambient temperature, diluted with ether, filtered through celite, and the filtrate was concentrated *en vaccuo*. The residue was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-30% EtOAc/Hexanes to give tert-butyl 5-nitro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl carbamate as a white foam.

Step 3: 8-nitrobenzo[f][1,7]naphthyridin-5-amine

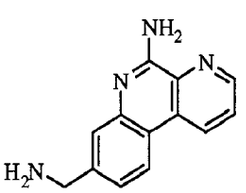
[000674] A solution of *tert*-butyl 5-nitro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from the previous step) (1.0 eq.) and 3-bromopicolinonitrile (1.0 eq.) in toluene (0.44 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction mixture was filtered to collect the precipitate. The precipitate was rinsed with EtOAc to give 8-nitrobenzo[f][1,7]naphthyridin-5-amine as a yellow solid.

Step 4: benzo[f][1,7]naphthyridine-5,8-diamine

[000675] A mixture of 8-nitrobenzo[f][1,7]naphthyridin-5-amine (from the previous step) (1.0 eq) and Pd/C (wet, 10% wt) in EtOH was stirred under H_2 balloon overnight. The reaction mixture was diluted with DCM. The insoluble solid was filtered off through celite, and the filtrate was concentrated *en vaccuo* to obtain a crude residue. The crude material was washed with acetone to give benzo[f][1,7]naphthyridine-5,8-diamine as an off white solid: ^{1}H NMR (methanol- d_4): δ 8.73 (dd, 1H), 8.71 (dd, 1H), 8.11 (d, 1H), 7.69 (dd, 1H), 6.86 (d, 1H), 6.82 (dd, 1H). LRMS [M+H] = 211.1.

Example 97

8-(aminomethyl)benzo[f][1,7]naphthyridin-5-amine



Step 1: 2-(tert-butoxycarbonylamino)-4-cyanophenylboronic acid

[000676] The titled compound was prepared according to the procedure described in Example 85

/ Step 1, but using 2-amino-4-cyanophenylboronic acid hydrochloride (commercially available) as the starting material. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-30% MeOH/DCM to give 2-(tert-butoxycarbonylamino)-4-cyanophenylboronic acid as an off white solid.

Step 2: 5-aminobenzo[f][1,7]naphthyridine-8-carbonitrile

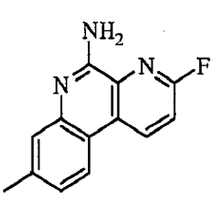
[000677] The titled compound was prepared according to the procedure described in Example 96 / Step 3, but using 2-(*tert*-butoxycarbonylamino)-4-cyanophenylboronic acid (from the previous step) as the starting material. The crude material was rinsed with 1:1 EtOAc/Hexanes to give 5-aminobenzo[f][1,7]naphthyridine-8-carbonitrile as a pale yellow solid.

Step 4: benzo[f][1,7]naphthyridine-5,8-diamine

[000678] A mixture of 8-nitrobenzo[f][1,7]naphthyridin-5-amine (from the previous step) (1.0 eq) and Raney Nickel (wet, 10% wt) in EtOH/ammonia (2:1) was stirred under H_2 balloon overnight. The reaction mixture was diluted with DCM. The insoluble solid was filtered off through celite, and the filtrate was concentrated *en vaccuo* to obtain a crude residue. The crude material was washed with 10% MeOH/DCM and 70% EtOAc/Hexanes to give benzo[f][1,7]naphthyridine-5,8-diamine as an off white solid: ^{1}H NMR (methanol- d_4): δ 8.97 (dd, 1H), 8.90 (dd, 1H), 8.41 (d, 1H), 7.83 (dd, 1H), 7.57 (d, 1H), 7.39 (dd, 1H), 3.96 (s, 2). LRMS [M+H] = 229.1.

Example 98

3-fluoro-8-methylbenzo[f][1,7]naphthyridin-5-amine



Step 1: 3-chloro-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000679] A solution of *tert*-butyl 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan -2-yl)phenylcarbamate (from Example 5 / Step 2) (1.0 eq.) and 3-bromo-6-chloropicolinonitrile (from Example 20 / Step 2) (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (5 mol%), and 2N aqueous sodium carbonate solution (2.0 eq.) in toluene/ethanol (2:1, 0.03 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and water. The two phases were separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a

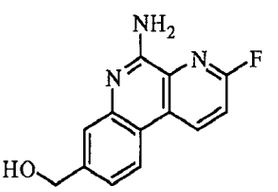
COMBIFLASH® system (ISCO) using 0-40% EtOAc/Hexanes to give 3-chloro-8-methylbenzo[f][1,7]naphthyridin-5-amine as a pale yellow solid.

Step 2: 3-fluoro-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000680] A mixture of 3-chloro-8-methylbenzo[f][1,7]naphthyridin-5-amine (from the previous step) (1.0 eq.) potassium fluoride (4.0 eq.), and 18-crown-6 (0.4 eq.) in NMP (0.1M) was heated in microwave reactor at 210 °C for 2 hours. After cooling to ambient temperature, the reaction redisue was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-30% EtOAc/Hexanes to give 3-fluoro-8-methylbenzo[f][1,7]naphthyridin-5-amine as a white solid. ^{1}H NMR (acetone- d_6): δ 9.20 (dd, 1H), 8.32 (d, 1H), 7.58 (dd, 1H), 7.46 (d, 1H), 7.21 (dd, 1H), 6.51 (br s, 2H), 2.47 (s, 3H). LRMS [M+H] = 228.1.

Example 99

(5-amino-3-fluorobenzo[f][1,7]naphthyridin-8-yl)methanol



Step 1: tert-butyl 5-((tert-butyldimethylsilyloxy)methyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate

[000681] The titled compound was prepared according to the procedure described in Example 93 / Step 1 and 2, but using 5-((*tert*-butyldimethylsilyloxy)methyl)-2-chloroaniline (commercially available) as the starting material. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-20% EtOAc/Hexanes to give tert-butyl 5-((tert-butyldimethylsilyloxy)methyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate as a white foam.

Step 2: 8-((tert-butyldimethylsilyloxy)methyl)-3-chlorobenzo[f][1,7]naphthyridin-5-amine

[000682] The titled compound was prepared according to the procedure described in Example 98 / Step 1, but using *tert*-butyl 5-((*tert*-butyldimethylsilyloxy)methyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from the previous step) as the starting material. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-15% EtOAc/Hexanes to give 8-((tert-butyldimethylsilyloxy)methyl)-3-chlorobenzo[f][1,7]naphthyridin-5-amine as a pale yellow solid.

Step 3: (5-amino-3-chlorobenzo[f][1,7]naphthyridin-8-yl)methanol

[000683] A solution of 8-((*tert*-butyldimethylsilyloxy)methyl)-3-chlorobenzo[f][1,7]

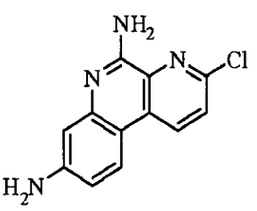
naphthyridin-5-amine (from the previous step) (1.0 eq.) and TBAF (1.1 eq.) in THF was stirred at ambient temperature overnight. The reaction was quenched with saturated $NaHCO_3$. The two phases were separated, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% MeOH/DCM to give (5-amino-3-chlorobenzo[f][1,7]naphthyridin-8-yl)methanol as a white solid.

Step 4: (5-amino-3-fluorobenzo[f][1,7]naphthyridin-8-yl)methanol

[000684] The titled compound was prepared according to the procedure described in Example 98 / Step 2, but using (5-amino-3-chlorobenzo[f][1,7]naphthyridin-8-yl)methanol (from the previous step) as the starting material. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-40% EtOAc/Hexanes to give (5-amino-3-fluorobenzo[f][1,7]naphthyridin-8-yl)methanol as a white solid. ^1H NMR (methanol- d_4): δ 9.15 (dd, 1H), 8.38 (d, 1H), 7.64 (d, 1H), 7.55 (dd, 1H), 7.41 (dd, 1H), 4.77 (s, 2H). LRMS [M+H] = 244.1.

Example 100

3-chlorobenzo[f][1,7]naphthyridine-5,8-diamine



Step 1: 3-chloro-8-nitrobenzo[f][1,7]naphthyridin-5-amine

[000685] The titled compound was prepared according to the procedure described in Example 98 / Step 1, but using *tert*-butyl 5-nitro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (commercially available) as the starting material. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-40% EtOAc/Hexanes to give 3-chloro-8-nitrobenzo[f][1,7]naphthyridin-5-amine as a pale yellow solid.

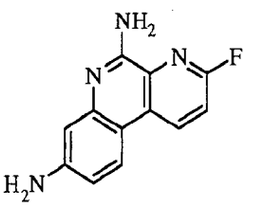
Step 2: 3-chlorobenzo[f][1,7]naphthyridine-5,8-diamine

[000686] A mixture of 8-nitrobenzo[f][1,7]naphthyridin-5-amine (from the previous step) (1.0 eq) and Raney Nickel (wet, 10% wt) in EtOH was stirred under H_2 balloon overnight. The reaction mixture was diluted with DCM. The insoluble solid was filtered off through celite, and the filtrate was concentrated *en vaccuo* to obtain a crude residue. The crude material was purified

by flash chromatography on a COMBIFLASH® system (ISCO) using 0-100% EtOAc/Hexanes to give 3-chlorobenzo[f][1,7]naphthyridine-5,8-diamine as a white solid. ^{1}H NMR (methanol- d_4): δ 8.75 (d, 1H), 8.08 (dd, 1H), 7.70 (d, 1H), 6.84-6.81 (m, 2H). LRMS [M+H] = 245.1.

Example 101

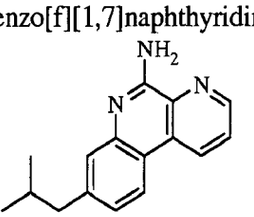
3-fluorobenzo[f][1,7]naphthyridine-5,8-diamine



[000687] The titled compound was prepared according to the procedure described in Example 98/Step 2, but using 3-chlorobenzo[f][1,7]naphthyridine-5,8-diamine (from Example 100) as the starting material. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-7% MeOH/DCM to give 3-fluorobenzo[f][1,7]naphthyridine-5,8-diamine as a white solid. ^{1}H NMR (methanol- d_4): δ 8.93 (dd, 1H), 8.09 (d, 1H), 7.44 (dd, 1H), 6.86-6.83 (m, 2H). LRMS [M+H] = 229.1.

Example 102

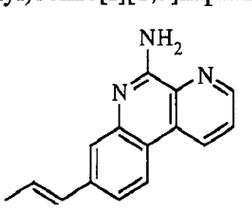
8-isobutylbenzo[f][1,7]naphthyridin-5-amine



[000688] 8-Isobutylbenzo[f][1,7]naphthyridin-5-amine was prepared from 5-aminobenzo[f][1,7]naphthyridine-8-carbaldehyde (from Example 87) with isopropyl(triphenyl)phosphonium bromide following the procedures described for Example 91 (wittig reaction) and Example 92 (reduction). ^{1}H NMR (acetone- d_6): δ 8.98(dd, 1H), 8.88 (dd, 1H), 8.35 (d, 1H), 7.82 (dd, 1H), 7.44 (d, 1H), 7.18 (dd, 1H), 6.73 (br s, 2H), 2.63 (d, 2H), 2.04-1.94 (m, 1H), 0.94 (d, 6H). LRMS [M+H] = 252.1.

Example 103

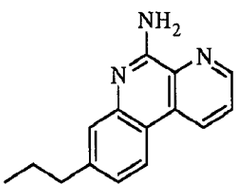
(*E*)-8-(prop-1-enyl)benzo[f][1,7]naphthyridin-5-amine



[000689] (*E*)-8-(prop-1-enyl)benzo[f][1,7]naphthyridin-5-amine was prepared from 5-aminobenzo[f][1,7]naphthyridine-8-carbaldehyde (from Example 87) with ethyl(triphenyl)phosphonium bromide following the procedures described for Example 91. ^{1}H NMR (acetone- d_6): δ 8.98(dd, 1H), 8.88 (dd, 1H), 8.36 (d, 1H), 7.83 (dd, 1H), 7.54 (d, 1H), 7.43 (dd, 1H), 6.67 (br s, 2H), 6.60-6.42 (m, 2H), 1.92 (dd, 3H). LRMS [M+H] = 236.1.

Example 104

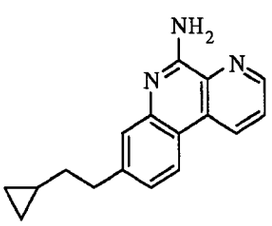
8-propylbenzo[f][1,7]naphthyridin-5-amine



[000690] 8-Propylbenzo[f][1,7]naphthyridin-5-amine was prepared from (*E*)-8-(prop-1-enyl)benzo[f][1,7]naphthyridin-5-amine (from Example 103) following the procedures described for Example 92. ^{1}H NMR (acetone- d_6): δ 8.99 (dd, 1H), 8.88 (dd, 1H), 8.35 (d, 1H), 7.83 (dd, 1H), 7.45 (d, 1H), 7.21 (dd, 1H), 6.64 (br s, 2H), 2.74 (t, 2H), 1.74 (qt, 2H), 0.98 (t, 3H). LRMS [M+H] = 238.1.

Example 105

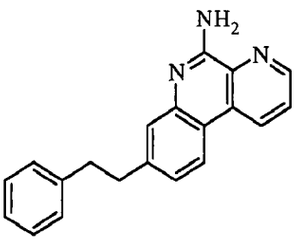
8-(2-cyclopropylethyl)benzo[f][1,7]naphthyridin-5-amine



[000691] 8-(2-Cyclopropylethyl)benzo[f][1,7]naphthyridin-5-amine was prepared from 5-aminobenzo[f][1,7]naphthyridine-8-carbaldehyde (from Example 87) with (cyclopropylmethyl)triphenylphosphonium bromide following the procedures described for Example 91 (wittig reaction) and Example 92 (reduction). ^{1}H NMR (acetone- d_6): δ 8.99(dd, 1H), 8.88 (dd, 1H), 8.35 (d, 1H), 7.83 (dd, 1H), 7.47 (d, 1H), 7.23 (dd, 1H), 6.64 (br s, 2H), 1.60 (q, 2H), 1.34-1.25 (m, 1H), 0.91-0.72 (m, 2H), 0.45-0.41 (m, 2H), 0.11-0.07 (m, 2H). LRMS [M+H] = 264.1.

Example 106

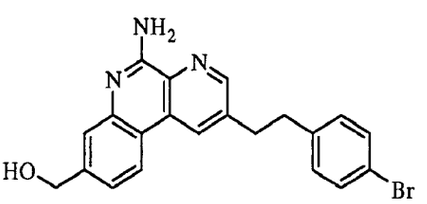
8-phenethylbenzo[f][1,7]naphthyridin-5-amine



[000692] 8-Phenethylbenzo[f][1,7]naphthyridin-5-amine was prepared from 5-aminobenzo[f][1,7]naphthyridine-8-carbaldehyde (from Example 87) with benzyltriphenylphosphonium bromide following the procedures described for Example 91 (wittig reaction) and Example 92 (reduction). ^{1}H NMR (acetone- d_6): δ 8.99 (dd, 1H), 8.88 (dd, 1H), 8.35 (d, 1H), 7.83 (dd, 1H), 7.49 (d, 1H), 7.29-7.15 (dd, 6H), 6.70 (br s, 2H), 3.10-3.00 (m, 4H). LRMS [M+H] = 300.1.

Example 107

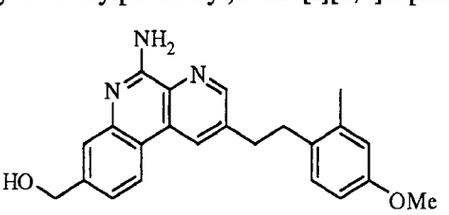
(5-amino-2-(4-bromophenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol



[000693] (5-Amino-2-(4-bromophenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol was prepared from (5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol (from Example 95) following the procedures described for Example 86. ^{1}H NMR (acetone- d_6): δ 8.81 (d, 1H), 8.72 (d, 1H), 8.40 (d, 1H), 7.68 (d, 1H), 7.39 (dd, 1H), 7.08 (d, 2H), 6.74 (d, 2H), 6.66 (br s, 2H), 4.49 (s, 2H), 3.21 (t, 2H), 3.03 (t, 2H). LRMS [M+H] = 408.1.

Example 108

(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol

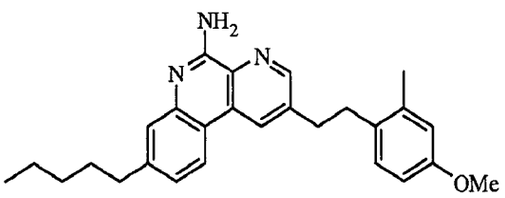


[000694] (5-Amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol was prepared from tert-butyl 5-((tert-butyldimethylsilyloxy)methyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (Example 99 / Step 1) and 3-chloro-5-((4-methoxy-2-methylphenyl)ethynyl)picolinonitrile (from Example 49 / Step 1) following the procedures described for Example 44 / Step 4 and deprotection of TBS group following the procedure describes from

Example 99 / Step 3. ^{1}H NMR (acetone- d_6): δ 8.79 (s, 1H), 8.73 (s, 1H), 8.35 (d, 1H), 7.61 (s, 1H), 7.33 (d, 1H), 7.09 (d, 1H), 6.75 (d, 1H), 6.68 (dd, 1H), 6.57 (br s, 2H), 4.47 (d, 2H), 4.32 (t, 1H), 3.58 (s, 3H), 3.17 (t, 2H), 3.04 (t, 2H), 2.30 (s, 3H). LRMS [M+H] = 374.2.

Example 109

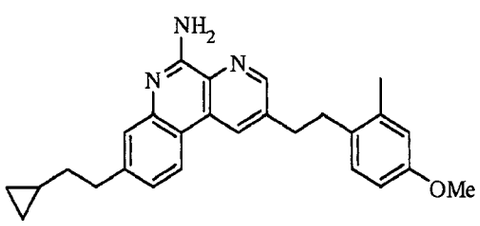
2-(4-methoxy-2-methylphenethyl)-8-pentylbenzo[f][1,7]naphthyridin-5-amine



and

Example 110

8-(2-cyclopropylethyl)-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine



Step 1: tert-butyl 5-bromo-2-chlorophenylcarbamate

[000695] The titled compound was prepared according to the procedure described in Example 5 / Step 1, but using 5-bromo-2-chloroaniline (commercially available) as the starting material. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-40% EtOAc/Hexanes to give tert-butyl 5-bromo-2-chlorophenylcarbamate as a pale yellow solid.

Step 2: (E)-tert-butyl 2-chloro-5-(2-cyclopropylvinyl)phenylcarbamate

[000696] A solution of *tert*-butyl 5-bromo-2-chlorophenylcarbamate (from the previous step) (1.0 eq.) and (*E*)-2-(2-cyclopropylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (commercially avalaible) (1.0 eq.) in toluene (0.2 M) was mixed with tetrakis(triphenyl-phosphine)palladium (5 mol%) and 2N aqueous potassium carbonate solution (2.0 eq.). The reaction was heated to 100°C and stirred overnight. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc and water. The two phases were separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-5% EtOAc/Hexanes to give (E)-tert-butyl 2-chloro-5-(2-

cyclopropylvinyl)phenylcarbamate as a pale yellow solid.

Step 3: (E)-tert-butyl 5-(2-cyclopropylvinyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate

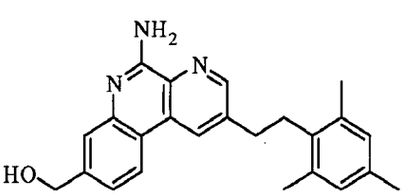
[000697] The titled compound was prepared according to the procedure described in Example 93 / Step 2, but using *(E)-tert*-butyl 2-chloro-5-(2-cyclopropylvinyl) phenylcarbamate (from prevous step) as the starting material.The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-10% EtOAc/Hexanes to give (E)-tert-butyl 5-(2-cyclopropylvinyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate as a pale yellow solid.

Step 4: 2-(4-methoxy-2-methylphenethyl)-8-pentylbenzo[f][1,7]naphthyridin-5-amine and 8-(2-cyclopropylethyl)-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine

[000698] The titled compounds were prepared according to the procedure described in Example 44 / Step 4 (Suzuki coupling) and 5 (reduction), but using *(E)-tert*-butyl 5-(2-cyclopropylvinyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from prevous step) and 3-chloro-5-((4-methoxy-2-methylphenyl)ethynyl) picolinonitrile (from Example 49 / Step1) as the starting material. The crude product was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-40% EtOAc/Hexanes to give Example 109 as a white solid: ^{1}H NMR (acetone-d_6): δ 8.76 (d, 1H), 8.70 (d, 1H), 8.29 (d, 1H), 7.44 (d, 1H), 7.18 (dd, 1H), 7.08 (d, 1H), 6.74 (d, 1H), 6.68 (dd, 1H), 6.59 (br s, 2H), 3.74 (s, 3H), 3.18 (t, 2H), 3.04 (t, 2H), 2.75 (t, 2H), 2.29 (s, 3H), 1.75-1.68 (m, 2H), 1.40-1.35 (m, 4H), 0.90 (s, 3H); LRMS [M+H] = 414.3; and Example 110 as an off white solid: ^{1}H NMR (acetone- d_6): δ 8.76 (d, 1H), 8.70 (d, 1H), 8.28 (d, 1H), 7.45 (d, 1H), 7.19 (dd, 1H), 7.08 (d, 1H), 6.74 (d, 1H), 6.67 (dd, 1H), 6.55 (br s, 2H), 3.73 (s, 3H), 3.16 (t, 2H), 3.03 (t, 2H), 2.29 (s, 3H), 1.60 (q, 2H), 1.29-1.28 (m, 1H), 0.89-0.74 (m, 2H), 0.44-0.41 (m, 2H), 0.10-0.07 (m, 2H). LRMS [M+H] = 412.3.

Example 111

(5-amino-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol

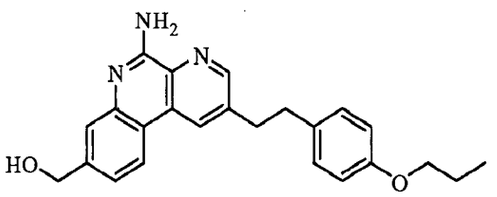


[000699] (5-Amino-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol was prepared from *tert*-butyl 5-((*tert*-butyldimethylsilyloxy)methyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from Example 99 / step 1), 2-ethynyl-1,3,5-trimethylbenzene

(commercially available) and 3-chloro-5-(mesitylethynyl)picolinonitrile (from Example 77 / step 1) following the procedures described for Example 44 / Step 4, Example 99 / step 3 (deprotecion of TBS) and Example 77 / step 3 (reduction). ^{1}H NMR (acetone- d_6): δ 8.77 (s, 2H), 8.34 (d, 1H), 7.61 (s, 1H), 7.33 (d, 1H), 6.84 (s, 2H), 6.60 (br s, 2H), 4.77 (d, 2H), 4.35 (t, 1H), 3.08 (s, 3H), 2.84 (s, 6H), 2.30-2.29 (m, 4H). LRMS [M+H] = 372.2.

Example 112

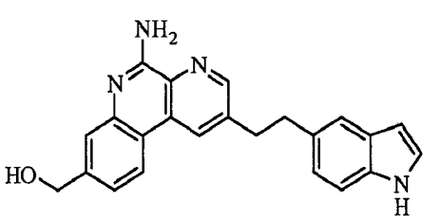
(5-amino-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol



[000700] (5-Amino-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol was prepared from 8-((*tert*-butyldimethylsilyloxy)methyl)-3-chlorobenzo[f][1,7] naphthyridin-5-amine (from Example 99 / step 1) and 3-chloro-5-(4-propoxyphenethyl) picolinonitrile (from Example 79 / step 2) following the procedures described for Example 44 / Step 4 and Example 99 / step 3 (deprotecion of TBS). ^{1}H NMR (acetone- d_6): δ 8.79 (d, 1H), 8.70 (d, 1H), 8.35 (d, 1H), 7.61 (d, 1H), 7.33 (dd, 1H), 7.17 (d, 2H), 6.83 (d, 2H), 6.57 (br s, 2H), 4.77 (d, 2H), 4.34 (t, 1H), 3.89 (t, 2H), 3.22 (t, 2H), 3.06 (t, 2H), 1.83-1.70 (m, 2H), 1.00 (t, 3H). LRMS [M+H] = 388.2.

Example 113

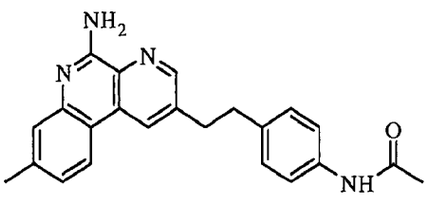
(2-(2-(1H-indol-5-yl)ethyl)-5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol



[000701] (2-(2-(1H-indol-5-yl)ethyl)-5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol was prepared from *tert*-butyl 5-((*tert*-butyldimethylsilyloxy)methyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from Example 99 / step 1) and 5-((1H-indol-5-yl)ethynyl)-3-chloropicolinonitrile (from Example 44 / step 3) following the procedures described for Example 44 / Step 4 and Example 99 / step 3 (deprotecion of TBS). ^{1}H NMR (acetone- d_6): δ 10.19 (t, 1H), 8.83 (d, 1H), 8.71 (d, 1H), 8.35 (d, 1H), 7.60 (d, 1H), 7.46 (d, 1H), 7.36-7.27 (m, 3H), 7.04 (dd, 1H), 6.57 (br s, 2H), 6.38 (dt, 1H), 4.77 (d, 2H), 4.36 (t, 1H), 3.29 (t, 2H), 3.19 (t, 2H). LRMS [M+H] = 369.2.

Example 114

N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide



Step 1: N-(4-ethynylphenyl)acetamide

[000702] To a solution of 4-ethynylaniline (commercially available) (1.0 eq.), and triethylamine (1.0 eq.) in methylene chloride (0.04 M), acetyl chloride (1.5 eq.) was added slowly. Then the reaction mixture was stirred at 0°C for 1 hour. After warmed to ambient temperature, the reaction mixture was diluted with ethyl acetate and water. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give N-(4-ethynylphenyl)acetamide as a white solid.

Step 2: N-(4-((5-chloro-6-cyanopyridin-3-yl)ethynyl)phenyl)acetamide

[000703] A solution of 3,5-dichloropicolinonitrile (1.0 eq.), N-(4-ethynylphenyl)acetamide (from the previous step) (1.0 eq.), bis(triphenyl-phosphine)palladium chloride (10 mol%), copper iodide (10 mol%), and triethylamine (5.0 eq.) in DMF (0.04 M) was stirred at 60°C for 4 hours. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and water. The two phases were separated. The organic layer was washed twice with water, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give N-(4-((5-chloro-6-cyanopyridin-3-yl)ethynyl)phenyl)acetamide as a white solid.

Step 3: N-(4-(2-(5-chloro-6-cyanopyridin-3-yl)ethyl)phenyl)acetamide

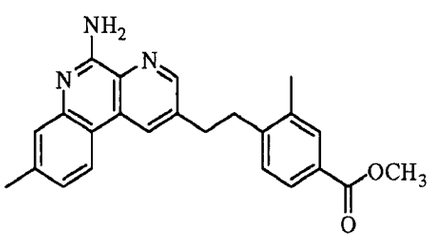
[000704] To a solution of N-(4-((5-chloro-6-cyanopyridin-3-yl)ethynyl)phenyl)acetamide (from the previous step) in ethyl acetate/methanol (1:4, 0.05 M) was added 10% wt palladium on carbon (0.2 eq.). Hydrogen gas was introduced via a ballon, and the reaction was stirred for 3 hours. The mixture was filtered through a pad of celite, washing with dichloromethane. The filtrate was concentrated *en vaccuo* and purified by a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give N-(4-(2-(5-chloro-6-cyanopyridin-3-yl)ethyl)phenyl)acetamide.

Step 4: N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide

[000705] A solution of N-(4-(2-(5-chloro-6-cyanopyridin-3-yl)ethyl)phenyl)acetamide (from the previous step) (1.0 eq.), tert-butyl 4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from Example 5 / Step 2) (1.5 eq.), Tris(dibenzylideneacetone)dipalladium(0) (10 mol%), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (20 mol%), and potassium phosphate (2.0 eq.) in n-butanol /H_2O (2.5:1, 0.04 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and water. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide as a white solid. ^1H NMR ($CDCl_3$): δ 8.51 (s, 1H), 8.32 (s, 1H), 8.01 (d, 1H), 7.44 (s, 1H), 7.33-7.36 (m, 2H), 7.03-7.19 (m, 3H), 5.98 (br, 2H), 3.07-3.11 (m, 2H), 2.94-2.98 (m, 2H), 2.44 (s, 3H), 2.10 (s, 3H). LRMS [M+H] = 371.2.

Example 115

methyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate



Step 1: methyl 3-methyl-4-((triethylsilyl)ethynyl)benzoate

[000706] A solution of methyl 4-bromo-3-methylbenzoate (1.0 eq.), triethyl(ethynyl)silane (1.0 eq.), bis(triphenyl-phosphine)palladium chloride (10 mol%), copper iodide (10 mol%), and triethylamine (5.0 eq.) in DMF (0.04 M) was stirred at 60°C for 4 hours. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and water. The two phases were separated. The organic layer was washed twice with water, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-50% ethyl acetate in hexane to give methyl 3-methyl-4-((triethylsilyl)ethynyl)benzoate as a white solid.

Step 2: methyl 4-ethynyl-3-methylbenzoate

[000707] To a solution of methyl 3-methyl-4-((triethylsilyl)ethynyl)benzoate (from the previous step) (1.0 eq.) in THF (0.2 M), was added TBAF (0.2 eq.) slowly at 0°C. Then the reaction mixture was stirred at 0°C for 1 hour. After warmed to ambient temperature, the reaction mixture

was diluted with ethyl acetate and water. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give methyl 4-ethynyl-3-methylbenzoate as a white solid.

Step 3: methyl 4-((5-chloro-6-cyanopyridin-3-yl)ethynyl)-3-methylbenzoate

[000708] A solution of 3,5-dichloropicolinonitrile (1.0 eq.), methyl 4-ethynyl-3-methylbenzoate (from the previous step) (1.0 eq.), bis(triphenyl-phosphine)palladium chloride (10 mol%), copper iodide (10 mol%), and triethylamine (5.0 eq.) in DMF (0.04 M) was stirred at 60°C for 4 hours. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and water. The two phases were separated. The organic layer was washed twice with water, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give methyl 4-((5-chloro-6-cyanopyridin-3-yl)ethynyl)-3-methylbenzoate as a white solid.

Step 4: methyl methyl 4-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)-3-methylbenzoate

[000709] A solution of methyl 4-((5-chloro-6-cyanopyridin-3-yl)ethynyl)-3-methylbenzoate (from the previous step) (1.0 eq.), tert-butyl 4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (From Example 5 / Step 2) (1.5 eq.), tris(dibenzylideneacetone)dipalladium(0) (10 mol%), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (20 mol%), and potassium phosphate (2.0 eq.) in n-butanol /H_2O (2.5:1, 0.04 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and water. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give methyl methyl-4-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)-3-methylbenzoate as a white solid.

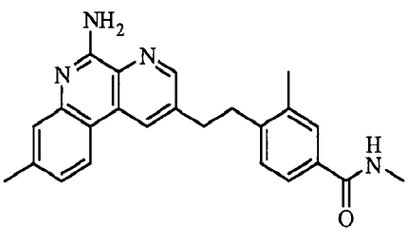
Step 5: methyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate

[000710] To a solution of methyl methyl 4-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)-3-methylbenzoate (from the previous step) in ethyl acetate/methanol (1:4, 0.05 M) was added 10% wt palladium on carbon (0.2 eq.). Hydrogen gas was introduced via a ballon, and the reaction was stirred for 3 hours. The mixture was filtered through a pad of celite, washing with

dichloromethane. The filtrate was concentrated *en vaccuo* and purified by a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give methyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate. ^{1}H NMR ($CDCl_3$): δ 8.61 (s, 1H), 8.40 (s, 1H), 8.09 (d, 1H), 7.83 (s, 1H), 7.81 (d, 1H), 7.54 (s, 1H), 7.18-7.20 (m, 2H), 6.17 (br, 2H), 3.92 (s, 3H), 3.10-3.16 (m, 4H), 2.53 (s, 3H), 2.36 (s, 3H). LRMS [M+H] = 386.2.

Example 116

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,3-dimethylbenzamide



Step 1: 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoic acid

[000711] A solution of methyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate (from Example 115) (1.0 eq.), and 1N sodium hydroxide (1.5 eq.) in methanol (0.04 M) was stirred at 60°C for 4 hours. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and water. The two phases were separated. The organic layer was washed twice with water, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-50% ethyl acetate in hexane to give 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoic acid as a white solid.

Step 2: 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoyl chloride

[000712] A solution of 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoic acid (from the previous step) in thionyl chloride was stirred at 60°C for 3 hour. After cooling to ambient temperature, the reaction mixture was concentrated *en vaccuo*. The crude material was used for next step without purification.

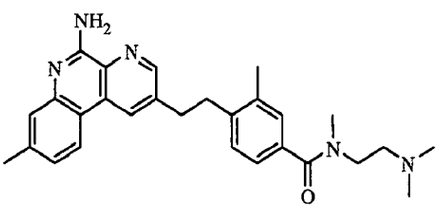
Step 3: 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,3-dimethylbenzamide

[000713] To a solution of 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoyl chloride (from the previous step) (Example 5) and triethylamine (2.5 eq.) in ether (0.05 M) was added methanamine (5.0 eq.). The reaction mixture was stirred for overnight. Then the reaction mixture was diluted with ethyl acetate and water. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was

purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,3-dimethylbenzamide as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.62 (s, 1H), 8.32 (s, 1H), 8.04 (d, 1H), 7.60 (s, 1H), 7.46-7.52 (m, 2H), 7.09-7.11 (m, 2H), 6.05 (br, 2H), 3.09-3.17 (m, 4H), 3.00 (d, 3H), 2.52 (s, 3H), 2.33 (s, 3H). LRMS [M+H] = 385.2.

Example 117

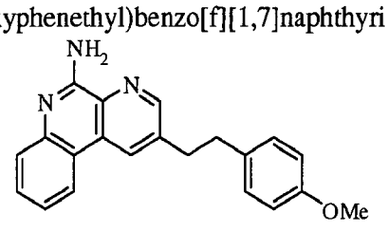
4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide



[000714] To a solution of 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoyl chloride (Example 116 / Step 2) and triethylamine (2.5 eq.) in ether (0.05 M) was added N^1,N^1,N^2-trimethylethane-1,2-diamine (5.0 eq.). The reaction mixture was stirred for overnight. Then the reaction mixture was diluted with ethyl acetate and water. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.66 (s, 1H), 8.37 (s, 1H), 8.07 (d, 1H), 7.63 (s, 1H), 7.09-7.30 (m, 4H), 3.90 (br, 2H), 3.01-3.19 (m, 4H), 3.08 (s, 6H), 2.72 (br, 5H), 2.52 (s, 3H), 2.33 (s, 3H). LRMS [M+H] = 456.3.

Example 118

2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine

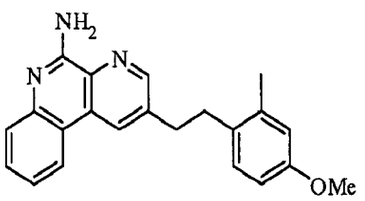


[000715] 2-(4-Methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine was prepared from 1-ethynyl-4-methoxybenzene (Example 116 / Step 2) following the procedures described for Example 45 / Steps 1 to 3. ^{1}H NMR ($CDCl_3$): δ 8.69 (s, 1H), 8.47 (s, 1H), 8.27 (d, 1H), 7.80 (d, 2H), 7.58-7.66

(m, 1H), 7.33-7.42 (m, 1H), 7.15 (d, 2H), 6.90 (d, 2H), 6.25 (br, 2H), 3.86 (s, 3H), 3.13-3.23 (m, 2H), 2.97-3.10 (m, 2H). LRMS [M+H] = 330.2.

Example 119

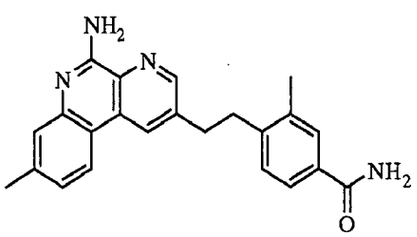
2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine



[000716] 2-(4-Methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine was prepared from 1-ethynyl-4-methoxy-2-methylbenzene (commercially available) following the procedures described for Example 45 / Step 1 to 3. 1H NMR ($CDCl_3$): δ 8.60 (s, 1H), 8.37 (s, 1H), 8.18 (d, 1H), 7.69 (d, 1H), 7.49-7.57 (m, 1H), 7.24-7.34 (m, 1H), 6.98 (d, 1H), 6.56-6.70 (m, 2H), 6.00 (br, 2H), 3.70 (s, 3H), 3.00-3.09 (m, 2H), 2.83-2.96 (m, 2H), 2.20 (s, 3H). LRMS [M+H] = 344.2.

Example 120

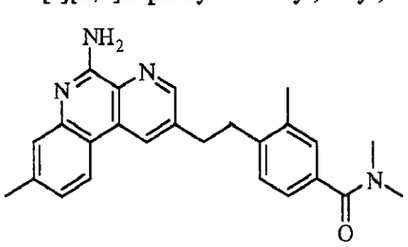
4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide



[000717] 4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoyl chloride (Example 116 / Step 2) and ammonia following the procedures described for Example 117. ^1H NMR ($CDCl_3$): δ 8.60 (s, 1H), 8.35 (s, 1H), 8.05 (d, 1H), 7.65 (s, 1H), 7.51-7.53 (m, 2H), 7.13-7.21 (m, 2H), 3.09-3.16 (m, 4H), 2.51 (s, 3H), 2.34 (s, 3H). LRMS [M+H] = 371.2

Example 121

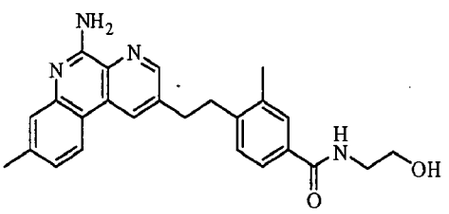
4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,N,3-trimethylbenzamide



[000718] 4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,N,3-trimethylbenzamide was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoyl chloride (Example 116 / Step 2) and dimethylamine following the procedures described for Example 117. ^{1}H NMR ($CDCl_3$): δ 8.68 (s, 1H), 8.32 (s, 1H), 8.04 (d, 1H), 7.66 (s, 1H), 7.31 (d, 1H), 7.06-7.18 (m, 3H), 3.08-3.19 (m, 4H), 2.96 (d, 3H), 2.54 (s, 3H), 2.33 (s, 3H), 2.05 (s, 3H). LRMS [M+H] = 399.2

Example 122

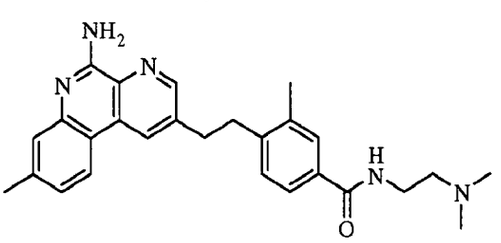
4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-hydroxyethyl)-3-methylbenzamide



[000719] 4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-hydroxyethyl)-3-methylbenzamide was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoyl chloride (Example 116 / Step 2) and 2-aminoethanol following the procedures described for Example 117. ^{1}H NMR ($CDCl_3$): δ 8.59 (s, 1H), 8.34 (s, 1H), 8.04 (d, 1H), 7.50-7.62 (m, 3H), 7.08-7.25 (m, 2H), 3.80 (t, 2H), 3.63 (t, 2H), 3.07-3.16 (m, 4H), 2.51 (s, 3H), 2.32 (s, 3H). LRMS [M+H] = 415.2

Example 123

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-3-methylbenzamide

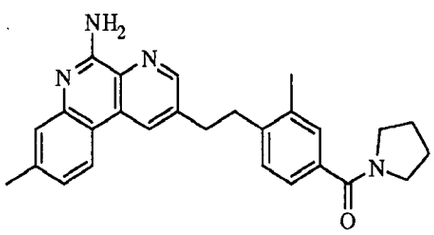


[000720] 4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-3-methylbenzamide was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoyl chloride (Example 116 / Step 2) and N^1,N^1-dimethylethane-1,2-diamine following the procedures described for Example 117. ^{1}H NMR (methanol- d_4): δ 8.60 (s, 1H), 8.39 (s, 1H), 8.08 (d, 1H), 7.68 (s, 1H), 7.57-7.59 (m, 2H), 7.19-7.22

(m, 2H), 3.57-3.61 (m, 2H), 3.07-3.16 (m, 4H), 2.64-2.67 (m, 2H), 2.52 (s, 3H), 2.38 (s, 6H), 2.35 (s, 3H). LRMS [M+H] = 442.3

Example 124

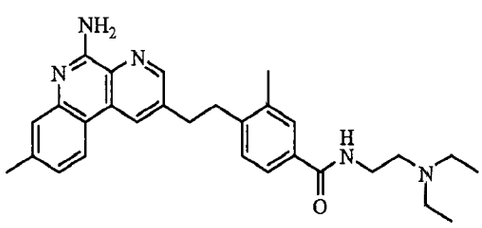
(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(pyrrolidin-1-yl)methanone



[000721] (4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(pyrrolidin-1-yl)methanone was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoyl chloride (Example 116 / Step 2) and pyrrolidine following the procedures described for Example 117. ^{1}H NMR (methanol- d_4): δ 8.60 (s, 1H), 8.42 (s, 1H), 8.09 (d, 1H), 7.34 (s, 1H), 7.23 (s, 1H), 7.05-7.15 (m, 3H), 3.49 (t, 2H), 3.27 (t, 2H), 3.05-3.17 (m, 4H), 2.42 (s, 3H), 2.26 (s, 3H), 1.88-1.91 (m, 2H), 1.73-1.77 (m, 2H). LRMS [M+H] = 425.2

Example 125

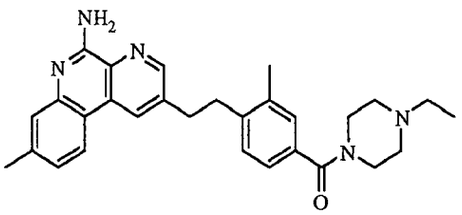
4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(diethylamino)ethyl)-3-methylbenzamide



[000722] 4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(diethylamino)ethyl)-3-methylbenzamide was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoyl chloride (Example 116 / Step 2) and N^1,N^1-diethylethane-1,2-diamine following the procedures described for Example 117. ^{1}H NMR (methanol- d_4): δ 8.55 (s, 1H), 8.48 (s, 1H), 8.10 (d, 1H), 7.56 (s, 1H), 7.47-7.50 (m, 1H), 7.33 (s, 1H), 7.10-7.14 (m, 2H), 3.44 (t, 2H), 3.25 (t, 2H), 3.08-3.14 (m, 4H), 2.62-2.72 (m, 4H), 2.42 (s, 3H), 2.27 (s, 3H), 1.05 (t, 6H). LRMS [M+H] = 470.3

Example 126

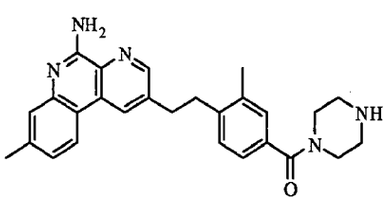
(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(4-ethylpiperazin-1-yl)methanone



[000723] (4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(4-ethylpiperazin-1-yl)methanone was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoyl chloride (Example 116 / Step 2) and 1-ethylpiperazine following the procedures described for Example 117. ^{1}H NMR (Methanol- d_4): δ 8.59 (s, 1H), 8.37 (s, 1H), 8.06 (d, 1H), 7.32 (s, 1H), 7.00-7.12 (m, 4H), 3.67 (br, 2H), 3.06-3.13 (m, 4H), 2.45 (br, 4H), 2.37 (q, 2H), 2.41 (s, 3H), 2.26 (s, 3H), 2.19 (br, 2H), 1.04 (t, 3H). LRMS [M+H] = 468.3

Example 127

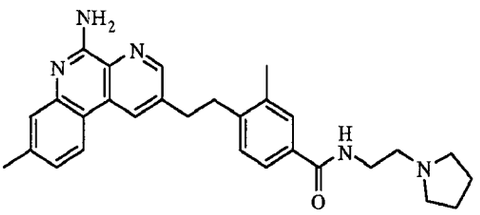
(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(piperazin-1-yl)methanone



[000724] (4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(piperazin-1-yl)methanone was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoyl chloride (Example 116 / Step 2) and piperazine following the procedures described for Example 117. ^{1}H NMR (methanol- d_4): δ 8.66 (s, 1H), 8.55 (s, 1H), 8.19 (d, 1H), 7.38 (s, 1H), 7.21-7.23 (m, 2H), 7.10-7.15 (m, 2H), 3.66 (br, 6H), 3.08-3.18 (m, 6H), 2.45 (s, 3H), 2.30 (s, 3H). LRMS [M+H] = 440.2

Example 128

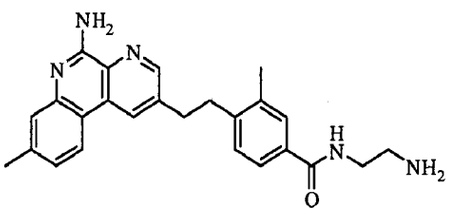
4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methyl-N-(2-(pyrrolidin-1-yl)ethyl)benzamide



[000725] 4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methyl-N-(2-(pyrrolidin-1-yl)ethyl)benzamide was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoyl chloride (Example 116 / Step 2) and 2-(pyrrolidin-1-yl)ethanamine following the procedures described for Example 117. ^{1}H NMR ($CDCl_3$): δ 8.58 (s, 1H), 8.38 (s, 1H), 8.07 (d, 1H), 7.64 (s, 1H), 7.51-7.55 (m, 2H), 7.12-7.20 (m, 2H), 6.26 (br, 2H), 3.61 (dd, 2H), 3.05-3.12 (m, 4H), 2.81 (t, 2H), 2.69 (br, 4H), 2.50 (s, 3H), 2.33 (s, 3H), 1.83-1.85 (m, 4H). LRMS [M+H] = 468.3

Example 129

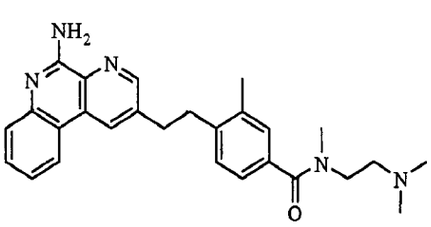
4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-aminoethyl)-3-methylbenzamide



[000726] 4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-aminoethyl)-3-methylbenzamide was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoyl chloride (Example 116 / Step 2) and ethane-1,2-diamine following the procedures described for Example 117. ^{1}H NMR ($CDCl_3$): δ 8.59 (s, 1H), 8.37 (s, 1H), 8.07 (d, 1H), 7.63 (s, 1H), 7.51 (br, 2H), 7.12-7.21 (m, 2H), 6.25 (br, 2H), 3.48-3.52 (m, 2H), 3.08-3.15 (m, 4H), 2.94 (t, 2H), 2.51 (s, 3H), 2.34 (s, 3H). LRMS [M+H] = 414.2

Example 130

4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide

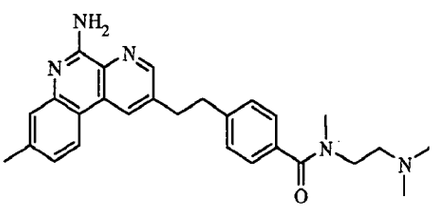


[000727] 4-(2-(5-Aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide was prepared from 4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-

methylbenzoyl chloride (Example 116 / Step 2) and N^1,N^1,N^2-trimethylethane-1,2-diamine following the procedures described for Example 117. ^{1}H NMR (methanol- d_4): δ 8.84 (s, 1H), 8.63 (s, 1H), 8.39 (d, 1H), 7.76-7.83 (m, 2H), 7.60-7.64 (m, 1H), 7.37 (s, 1H), 7.19-7.29 (m, 2H), 3.96 (t, 2H), 3.48 (t, 2H), 3.32 (t, 2H), 3.20 (t, 2H),3.09 (s, 3H), 3.06 (s, 6H), 2.42 (s, 3H). LRMS [M+H] = 442.3

Example 131

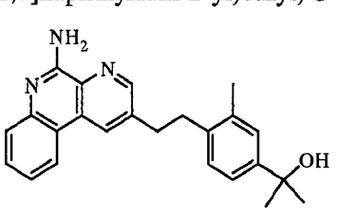
4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N-methylbenzamide



[000728] 4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N-methylbenzamide was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoyl chloride (Example 116 / Step 2) and N^1,N^1,N^2-trimethylethane-1,2-diamine following the procedures described for Example 117. ^{1}H NMR ($CDCl_3$): δ 8.64 (s, 1H), 8.36 (s, 1H), 8.05 (d, 1H), 7.60 (s, 1H), 7.41 (d, 2H), 7.31 (d, 1H), 7.21 (d, 2H), 3.91 (t, 2H), 3.44 (t, 2H), 3.25 (t, 2H), 3.12 (t, 2H),3.03 (s, 3H), 3.01 (s, 6H), 2.53 (s, 3H). LRMS [M+H] = 442.3

Example 132

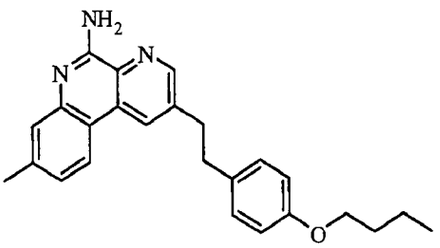
2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol



[000729] 2-(4-(2-(5-Aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol was prepared following the procedures described for Example 78, but using methyl 4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate which was prepared analogous to Example 115 but using tert-butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate in Step 4. LRMS [M+H] = 372.2

Example 133

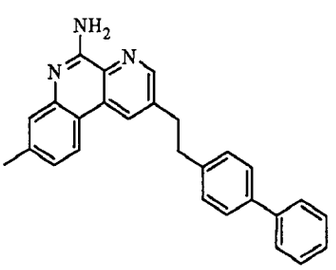
2-(4-butoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



[000730] 2-(4-Butoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared following the procedures described for Example 45 / Steps 1 to 3, but using 1-butoxy-4-ethynylbenzene (commercially available) with 3,5-dichloropicolinonitrile (commercially available) in step 1. ^{1}H NMR (Acetone- d_6): δ 8.75 (s, 1H), 8.68 (s, 1H), 8.28 (d, 1H), 7.42 (s, 1H), 7.10-7.18 (m, 3H), 6.84 (d, 2H), 6.58 (br, 2H), 3.94 (t, 2H), 3.21 (t, 2H), 3.05 (t, 2H), 2.46 (s, 3H), 1.65-1.75 (m, 2H), 1.41-1.58 (m, 2H), 0.94 (s, 3H). LRMS [M+H] = 386.2.

Example 134

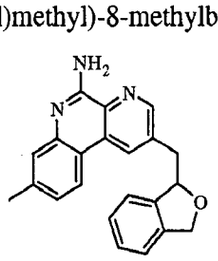
2-(2-(biphenyl-4-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



[000731] 2-(2-(Biphenyl-4-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared following the procedures described for Example 45 / Steps 1 to 3, but using 4-ethynylbiphenyl (commercially available) with 3,5-dichloropicolinonitrile (commercially available) in Step 1. ^{1}H NMR (Acetone- d_6): δ 8.80 (s, 1H), 8.75 (s, 1H), 8.26 (d, 2H), 7.55-7.69 (m, 4H), 7.30-7.46 (m, 4H), 7.13 (d, 2H), 6.58 (br, 2H), 3.30 (t, 2H), 3.18 (t, 2H), 2.45 (s, 3H). LRMS [M+H] = 390.2

Example 135

2-((1,3-dihydroisobenzofuran-1-yl)methyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



Step1: 2-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)phenyl)methanol

[000732] 2-((5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)phenyl)methanol was prepared following the procedures described for Example 45 / Steps 1 to 2, but using (2-

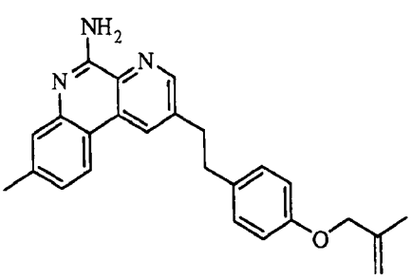
ethynylphenyl)methanol (commercially available) with 3,5-dichloropicolinonitrile (commercially available) in Step 1.

Step2: 2-((1,3-dihydroisobenzofuran-1-yl)methyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000733] To a solution of 2-((5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethynyl)phenyl)methanol (1.0 equiv.) (from the previous step) in ethanol (0.05 M) was added 10% wt palladium on carbon (0.2 equiv. by weight). Hydrogen gas was then introduced via a balloon, and the reaction was allowed to stir for 18 hours. At this point, the mixture was filtered through a pad of celite, washing with methanol. The volatiles were removed *in vacuo* and the resulting residue was purified by a COMBIFLASH® system (ISCO) using 0-60% ethyl acetate in hexanes to give 2-((1,3-dihydroisobenzofuran-1-yl)methyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine as a solid. ^{1}H NMR (Acetone- d_6): δ 8.78 (s, 1H), 8.74 (s, 1H), 8.24 (d, 2H), 7.40-7.44 (m, 2H), 7.20-7.34 (m, 3H), 6.61 (br, 2H), 5.63-5.69 (m, 1H), 4.89-5.00 (dd, 2H), 3.51-3.56 (dd, 1H), 3.28-3.34 (dd, 1H), 2.46 (s, 3H). LRMS [M+H] = 342.1

Example 136

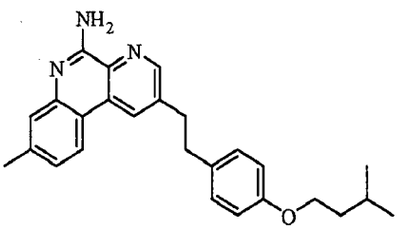
8-methyl-2-(4-(2-methylallyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine



[000734] To a solution of 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol (from Example 170) (1.0 equiv.) in dimethylformamide (0.10 M) was added anhydrous potassium carbonate (1.5 euiv.) followed by methallyl bromide (1.2 equiv.). The resulting mixture was allowed to stir for 18 hours at 100 °C. After cooling to ambient temperature, the mixture was diluted with ethyl acetate and water. The biphasic layers were separated and the aqueous layer was washed twice with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and the volatiles were removed *in vacuo*. The resulting residue was purified by a COMBIFLASH® system (ISCO) using 0-60% ethyl acetate in hexanes to provide 8-methyl-2-(4-(2-methylallyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine as a solid. ^{1}H NMR (Acetone- d_6): δ 8.75 (s, 1H), 8.68 (s, 1H), 8.27 (d, 1H), 7.41 (s, 1H), 7.12-7.19 (m, 3H), 6.87 (d, 2H), 6.60 (br, 2H), 5.06 (s, 1H), 4.93 (s, 1H), 4.43 (s, 2H), 3.20 (t, 2H), 3.05 (t, 2H), 2.45 (s, 3H), 1.79 (s, 3H). LRMS [M+H] = 384.2

Example 137

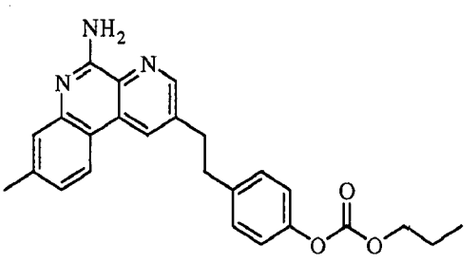
2-(4-(isopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



[000735] 2-(4-(Isopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol (from Example 170) following the procedure described for Example 136, but using 1-bromo-3-methylbutane. ^{1}H NMR (Acetone- d_6): δ 8.72 (s, 1H), 8.69 (s, 1H), 8.26 (d, 1H), 7.43 (s, 1H), 7.12-7.18 (m, 3H), 6.84 (d, 2H), 6.50 (br, 2H), 3.98 (t, 2H), 3.21 (t, 2H), 3.06 (t, 2H), 2.46 (s, 3H), 1.78-1.87 (m, 1H), 1.61-1.67 (dd, 2H), 0.96 (s, 3H), 0.95 (3H). LRMS [M+H] = 400.2

Example 138

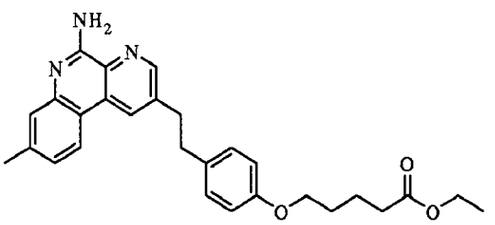
4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl propyl carbonate



[000736] To a solution of 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol (from Example 170) (1.0 equiv.) and triethyl amine (2 equiv.) in dichloromethane (0.10 M) at 0 °C was added ethyl chloroformate (1.2 equiv.). The resulting mixture was allowed to stir for 30 minutes at 0 °C, after which it was diluted with water and dichloromethane. The biphasic layers were separated and the aqueous layer was washed twice with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4 and the volatiles were removed *in vacuo*. The resulting residue was purified by a COMBIFLASH® system (ISCO) using 0-50% ethyl acetate in hexanes to provide 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl ethyl carbonate as a solid. ^{1}H NMR (Acetone- d_6): δ 8.78 (s, 1H), 8.73 (s, 1H), 8.28 (d, 1H), 7.43 (s, 1H), 7.33 (d, 2H), 7.10-7.17 (m, 3H), 6.64 (br, 2H), 4.18 (t, 2H), 3.25 (t, 2H), 3.14 (t, 2H), 2.45 (s, 3H), 1.68-1.77 (m, 2H), 0.97 (t, 3H). LRMS [M+H] = 416.2

Example 139

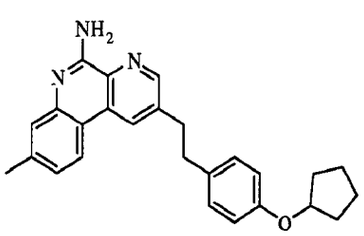
ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoate



[000737] To a solution of 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol (from Example 170) (1.0 equiv.) in dimethylformamide (0.10 M) 22 °C was added 60% dispersion of sodium hydride in mineral oil (1.5 euiv.) and the resulting mixture was allowed to stir for 30 min. At this point, ethyl 5-bromopentanoate (1.2 equiv.) was added to this mixture. The reaction mixture was then allowed to stir for 18 hours. after which it was diluted with ethyl acetate and water. The biphasic layers were separated and the organic layer was washed twice with water. The organic layer was dried over anhydrous Na_2SO_4 and the volatiles were removed *in vacuo*. The resulting residue was purified by RP-HPLC using a 10-50% MeCN in water gradient. The resulting trifluoroacetate salt was then converted to the free base form by utilizing a StratoSpheres™ PL-SO3H SPE ion exchange resin, delivering ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoate as a solid. ^{1}H NMR (Acetone- d_6): δ 8.80 (s, 1H), 8.74 (s, 1H), 8.33 (d, 1H), 7.47 (s, 1H), 7.24 (d, 1H), 7.17 (d, 2H), 6.85 (d, 2H), 4.10 (q, 2H), 3.97 (t, 2H), 3.25 (t, 2H), 3.07 (t, 2), 2.50 (s, 3H), 2.37 (t, 3H), 1.74-1.84 (m, 4H), 1.21 (t, 3H). LRMS [M+H] = 458.2

Example 140

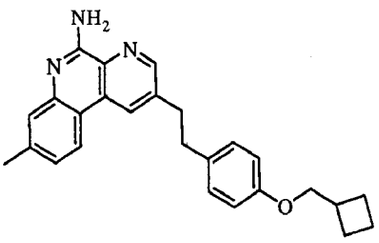
2-(4-(cyclopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



[000738] 2-(4-(Cyclopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol (from Example 170) following the procedure described for Example 136, but using bromocyclopentane. ^{1}H NMR (Acetone- d_6): δ 8.75 (d, 2H), 8.30 (d, 1H), 7.45 (s, 1H), 7.20 (d, 1H), 7.14 (d, 2H), 6.79 (d, 2H), 4.73-4.81 (m, 1H), 3.22 (t, 2H), 3.05 (t, 2H), 2.47 (s, 3H), 1.85-1.96 (m, 2H), 1.70-1.79 (m, 4H), 1.56-1.64 (m, 2H). LRMS [M+H] = 398.2

Example 141

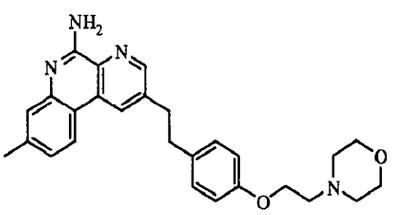
2-(4-(cyclobutylmethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



[000739] 2-(4-(Cyclobutylmethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol (from Example 170) following the procedure described for Example 136, but using (bromomethyl)cyclobutane. ^{1}H NMR (Acetone- d_6): δ 8.79 (s, 1H), 8.73 (s, 1H), 8.33 (d, 1H), 7.47 (s, 1H), 7.26 (d, 1H), 7.16 (d, 2H), 6.82 (d, 2H), 3.90 (d, 2H), 3.23 (t, 2H), 3.06 (t, 2H), 2.68-2.79 (m, 1H), 2.49 (s, 3H), 2.05-2.14 (m, 2H), 1.80-1.98 (m, 4H). LRMS [M+H] = 398.2

Example 142

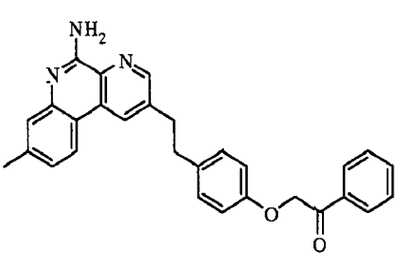
8-methyl-2-(4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine



[000740] 8-Methyl-2-(4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol (from Example 170) following the procedure described for Example 139, but using 4-(2-bromoethyl)morpholine. ^{1}H NMR (Acetone- d_6): δ 8.78 (s, 1H), 8.72 (s, 1H), 8.30 (d, 1H), 7.46 (s, 1H), 7.17-7.24 (m, 3H), 6.85 (d, 2H), 4.08 (t, 2H), 3.56-3.62 (m, 4H), 3.45-3.53 (m, 2H), 3.24 (t, 2H), 3.07 (t, 2H), 2.73 (t, 2H), 2.52-2.56 (m, 2H), 2.49 (s, 3H). LRMS [M+H] = 443.2

Example 143

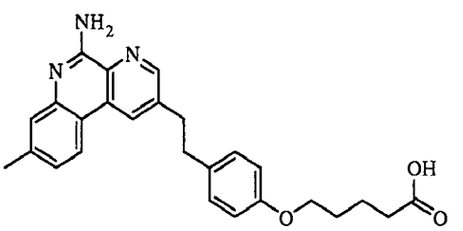
2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-1-phenylethanone



[000741] 2-(4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-1-phenylethanone was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol (from Example 170) following the procedure described for Example 139, but using 2-bromo-1-phenylethanone. ^{1}H NMR (Acetone- d_6): δ 8.76 (s, 1H), 8.71 (s, 1H), 8.27 (d, 1H), 8.06 (d, 2H), 7.67 (t, 1H), 7.57 (t, 2H), 7.43 (s, 1H), 7.17 (d, 3H), 6.90 (d, 2H), 5.45 (s, 2H), 3.21 (t, 2H), 3.06 (t, 2H), 2.45 (s, 3H). LRMS [M+H] = 448.2

Example 144

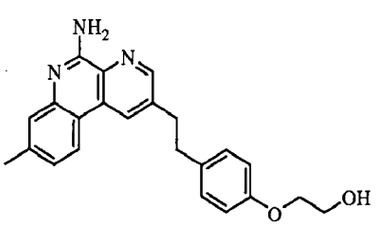
5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoic acid



[000742] To a solution of ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoate (1.0 equiv.) (from Example 139) in ethanol (0.10 M) was added anhydrous sodium hydroxide (2.0 equiv.) and the resulting mixture was allowed to stir at 80 °C for 2 hours. After cooling to ambient temperature, the mixture was diluted with ethyl acetate and water. The biphasic layers were separated and the aqueous layer was washed twice with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and the volatiles were removed *in vacuo*. The resulting residue was purified by a COMBIFLASH® system (ISCO) using 0-10% methanol in dichloromethane to furnish 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoic acid as a solid. ^{1}H NMR (Methanol- d_4): δ 8.61 (s, 1H), 8.57 (s, 1H), 8.20 (d, 1H), 7.40 (s, 1H), 7.20 (d, 1H), 7.07 (d, 2H), 6.81 (d, 2H), 3.93 (t, 2H), 3.18 (t, 2H), 3.00 (t, 2H), 2.48 (s, 3H), 2.25 (t, 2H), 1.74-1.81 (m, 2H), 0.86-0.96 (m, 2H). LRMS [M+H] = 430.2

Example 145

2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)ethanol



Step 1: 2-(4-(2-(tert-butyldimethylsilyloxy)ethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

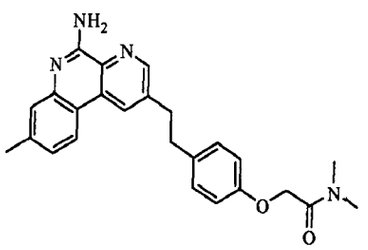
[000743] 2-(4-(2-(Tert-butyldimethylsilyloxy)ethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol (from Example 170) following the procedure described for Example 139, but using (2-bromoethoxy)(tert-butyl)dimethylsilane.

Step 2: 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)ethanol

[000744] To a solution of 2-(4-(2-(tert-butyldimethylsilyloxy)ethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine (from the previous step) (1.0 equiv.) in tetrahydrofuran (0.10 M) was added a 1.0 M solution of tetrabutylammonium fluoride (5 equiv.) in THF and the resulting mixture was allowed to stir at 22 °C for 2 hours. At this point, the mixture was diluted with ethyl acetate and water. The biphasic layers were separated and the aqueous layer was washed twice with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and the volatiles were removed *in vacuo*. The resulting residue was purified by a COMBIFLASH® system (ISCO) using 0-10% methanol in dichloromethane to furnish 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)ethanol as a solid. ^{1}H NMR (Acetone- d_6): δ 8.76 (s, 1H), 8.67 (s, 1H), 8.28 (d, 1H), 7.40 (s, 1H), 7.15 (t, 3H), 6.84 (d, 2H), 6.54 (br, 2H), 4.00 (t, 2H), 3.83 (t, 2H), 3.21 (t, 2H), 3.05 (t, 2H), 2.45 (s, 3H). LRMS [M+H] = 374.2

Example 146

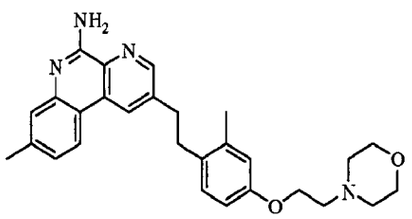
2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-N,N-dimethylacetamide



[000745] 2-(4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-N,N-dimethylacetamide was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol (from Example 170) and following the procedure described for Example 139, but using 2-bromo-*N,N*-dimethylacetamide. ^{1}H NMR (Acetone- d_6): δ 8.75 (s, 1H), 8.70 (s, 1H), 8.28 (d, 1H), 7.40 (s, 1H), 7.18 (t, 3H), 6.87 (d, 2H), 6.56 (br, 2H), 4.72 (s, 2H), 3.20 (t, 2H), 3.07 (s, 3H), 3.05 (t, 2H), 2.87 (s, 3H), 2.45 (s, 3H). LRMS [M+H] = 415.2

Example 147

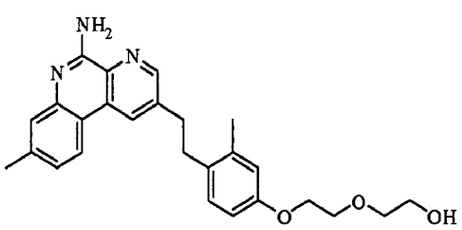
8-methyl-2-(2-methyl-4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine



[000746] 8-Methyl-2-(2-methyl-4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine was prepared following an analogous procedure to the preparation described for Example 139, but using 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol (from Example 50) and 4-(2-bromoethyl)morpholine. ^{1}H NMR (Acetone- d_6): δ 8.73 (d, 2H), 8.26 (d, 1H), 7.44 (s, 1H), 7.17 (d, 1H), 7.05 (d, 1H), 6.76 (s, 1H), 6.67 (d, 1), 4.04-4.08 (m, 3H), 3.60-3.62 (m, 4H), 3.30 (s, 1H), 3.16 (t, 2H), 3.04 (t, 2H), 2.71 (t, 2H), 2.50-2.52 (m, 2H), 2.47 (s, 3H), 2.28 (s, 3H). LRMS [M+H] = 457.3

Example 148

2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethanol



Step 1: 2-(4-(2-(2-(tert-butyldimethylsilyloxy)ethoxy)ethoxy)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000747] 2-(4-(2-(2-(Tert-butyldimethylsilyloxy)ethoxy)ethoxy)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared following an analogous procedure to the preparation described for Example 145 / Step 1, but using 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol (from Example 50) with tert-butyl(2-(2-chloroethoxy)ethoxy)dimethylsilane.

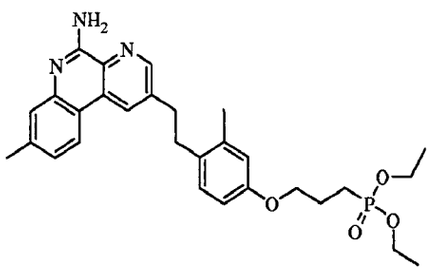
Step 2: 2-(2-(4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethanol

[000748] 2-(2-(4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethanol was prepared from 2-(4-(2-(2-(tert-butyldimethylsilyloxy)ethoxy)ethoxy)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine (from the previous step) following the procedures described for Example 145 / Step 2. ^{1}H NMR (Acetone- d_6): δ 8.74 (s, 1H), 8.69 (s, 1H), 8.27 (d, 1H), 7.41 (s, 1H), 7.14 (d, 1H), 7.06 (d,

1H), 6.75 (s, 1H), 6.69 (d, 1), 6.54 (br, 2H), 4.07 (t, 2H), 3.79 (t, 2H), 3.64 (t, 2H), 3.59 (t, 2H), 3.16 (t, 2H), 3.03 (t, 2H), 2.45 (s, 3H), 2.29 (s, 3H). LRMS [M+H] = 432.2

Example 149

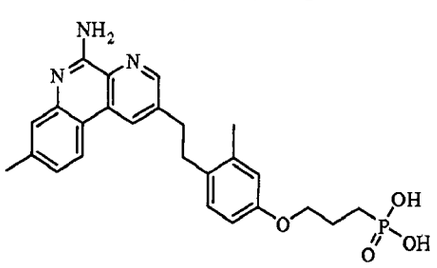
diethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonate



[000749] Diethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonate was prepared following an analogous procedure to the preparation described for Example 139, but using 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol (from Example 50) with diethyl 3-bromopropylphosphonate. ^{1}H NMR (Acetone- d_6): δ 9.52 (s, 1H), 9.47 (s, 1H), 9.03 (d, 1H), 8.21 (s, 1H), 7.93 (d, 1H), 7.84 (d, 1H), 7.60 (br, 2H), 7.53 (s, 1), 7.45 (d, 1H), 4.76-4.91 (m, 6H), 3.93 (t, 2H), 3.81 (t, 2H), 3.24 (s, 3H), 3.06 (s, 3H), 2.76-2.86 (m, 2H), 2.61-2.72 (m, 2H), 2.07 (t, 6H). LRMS [M+H] = 522.2

Example 150

3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonic acid

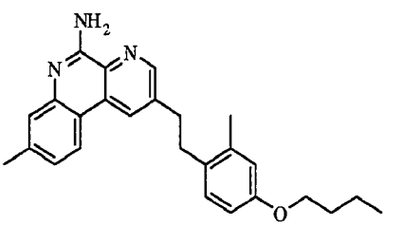


[000750] A 12 N solution of hycrochloric acid (0.10 M) was added to diethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonate (from Example 149) and the resulting mixture was allowed to stir at 100 °C for 18 hours. At this point, hydrochloric acid was removed under reduced pressure and the resulting residue was purified by RP-HPLC using a 10-50% MeCN in water gradient. The resulting trifluoroacetate salt was then converted to the free base form by the addition of a saturated aqueous solution of sodium bicarbonate, followed by washing three times with ethyl acetate. The combined organic layers were dried with anhydrous

Na_2SO_4, and the volatiles were removed *in vacuo* to deliver 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonic acid as a solid. ^1H NMR (Dimethylsulfoxide- d_6): δ 9.72 (br, 1H), 9.01 (s, 1H), 8.96 (br, 1H), 8.85 (s, 1H), 8.54 (d, 1H), 7.54 (s, 1H), 7.42 (d, 1H), 7.08 (d, 1), 6.74 (s, 1H), 6.66 (d, 1H), 3.95 (t, 2H), 3.14 (t, 2H), 2.97 (t, 2H), 2.50 (s, 3H), 2.27 (s, 3H), 1.81-1.91 (m, 2H), 1.56-1.67 (m, 2H). LRMS [M+H] = 466.2

Example 151

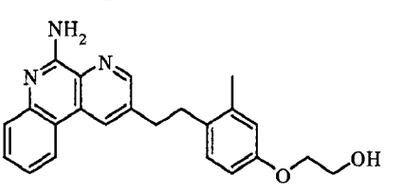
2-(4-butoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



[000751] 2-(4-Butoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared following an analogous procedure to the preparation described for Example 139, but using 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol (from Example 50) with1-bromobutane. ^1H NMR (Acetone- d_6): δ 8.75 (s, 1H), 8.71 (s, 1H), 8.28 (d, 1H), 7.43 (s, 1H), 7.15 (d, 1H), 7.07 (d, 1H), 6.75 (s, 1H), 6.69 (d, 1H), 6.54 (br, 2H) 3.95 (t, 2H), 3.16 (t, 2H), 3.04 (t, 2H), 2.47 (s, 3H), 2.30 (s, 3H), 1.69-1.77 (m, 2H), 1.43-1.54 (m, 2H), 0.97 (t, 3H). LRMS [M+H] = 400.2

Example 152

2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol



Step 1: 4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol

[000752] 4-(2-(5-Aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol was prepared following an analogous procedure to the preparation described for Example 145, but using 2-(4-Methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine (from Example 119).

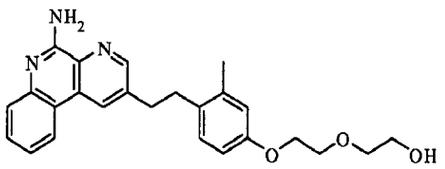
Step 2: 2-(4-(2-(5-Aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol

[000753] 2-(4-(2-(5-Aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol was prepared from 4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol (from the

previous step) following the procedures described for Example 145 / Steps 1 to 2. LRMS [M+H] = 374.2

Example 153

2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol



Step 1: 4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol

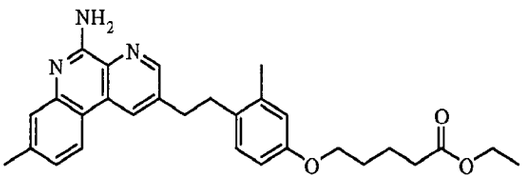
[000754] 4-(2-(5-Aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol was prepared following an analogous procedure to the preparation described for Example 50, but using 2-(4-Methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine (from Example 119).

Step 2: 2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol

[000755] 2-(4-(2-(5-Aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol was prepared following the procedures described for Example 148 / Steps 1 to 2. LRMS [M+H] = 418.2

Example 154

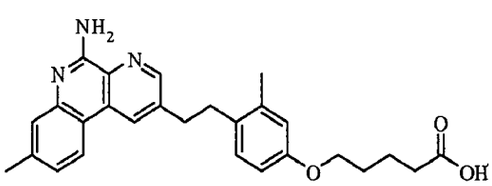
ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoate



[000756] Ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoate was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol (from Example 50) following the procedure described for Example 139, but using ethyl 5-bromopentanoate . ^{1}H NMR (CDCl3): δ 8.64 (s, 1H), 8.27 (s, 1H), 8.02 (d, 1H), 7.66 (s, 1H), 7.32 (d, 1H), 6.91 (d, 1H), 6.66 (s, 1H), 6.63 (d, 1H), 4.13 (q, 2H), 3.93 (t, 2H), 3.14 (t, 2H), 2.99 (t, 2H), 2.54 (s, 3H), 2.38 (t, 2H), 2.25 (s, 3H), 1.79-1.83 (m, 4H), 1.26 (t, 3H). LRMS [M+H] = 472.3

Example 155

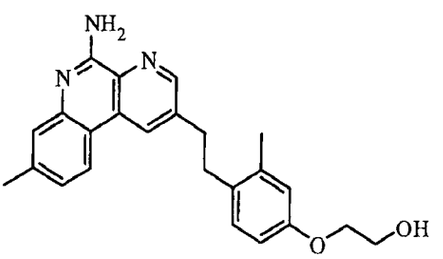
5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoic acid



[000757] 5-(4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoic acid was prepared from ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoate (from the previous step) following the procedure described for Example 144. ^{1}H NMR (CDCl3): δ 8.52 (s, 1H), 8.27 (s, 1H), 8.02 (d, 1H), 7.65 (s, 1H), 7.32 (d, 1H), 6.86 (d, 1H), 6.72 (s, 1H), 6.63 (d, 1H), 3.95 (t, 2H), 3.15 (t, 2H), 2.99 (t, 2H), 2.54 (s, 3H), 2.45 (t, 2H), 2.23 (s, 3H), 1.79-1.83 (m, 4H). LRMS [M+H] = 444.2

Example 156

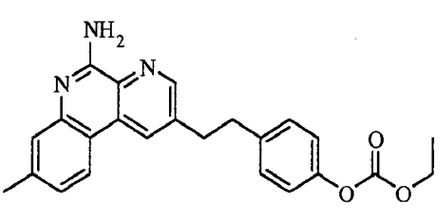
2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol



[000758] 2-(4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol was prepared following the procedures described for Example 145 / Steps 1 to 2, but using 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol (from Example 50). ^{1}H NMR (Acetone- d_6): δ 8.76 (s, 1H), 8.69 (s, 1H), 8.28 (d, 1H), 7.40 (s, 1H), 7.15 (d, 1H), 7.09 (d, 1H), 6.75 (s, 1H), 6.68 (d, 1H), 6.57 (br, 2H), 4.00 (t, 2H), 3.79-3.88 (m, 2H), 3.17 (t, 2H), 3.04 (t, 2H), 2.46 (s, 2H), 2.29 (s, 2H). LRMS [M+H] = 388.5.

Example 157

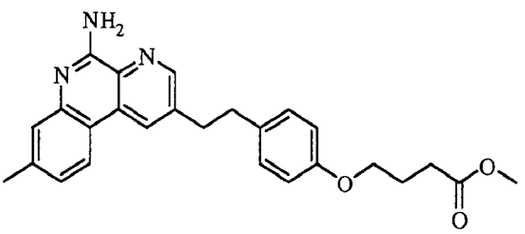
4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl ethyl carbonate



[000759] 4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl ethyl carbonate was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol (from Example 170) following the procedure described for Example 138, but using ethyl carbonochloridate. LRMS [M+H] = 402.2

Example 158

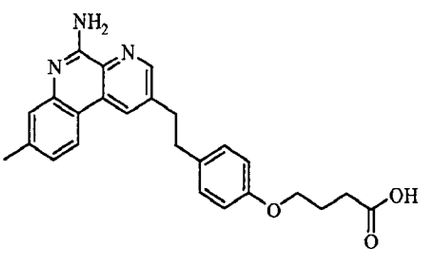
methyl 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoate



[000760] Methyl 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoate was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol (from Example 170) following the procedure described for the preparation of Example 139, but using methyl 4-bromobutanoate. ^{1}H NMR (Acetone- d_6): δ 8.74 (s, 1H), 8.67 (s, 1H), 8.24 (d, 1H), 7.39 (s, 1H), 7.09-7.19 (m, 3H), 6.82 (d, 2H), 6.53 (br, 2H), 3.97 (t, 2H), 3.60 (s, 3H), 3.19 (t, 2H), 3.04 (t, 2H), 2.48 (t, 2H), 2.44 (s, 3H), 0.84-0.91 (m, 2H). LRMS [M+H] = 430.2.

Example 159

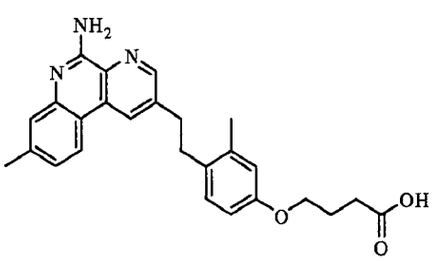
4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoic acid



[000761] 4-(4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoic acid was prepared from methyl 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoate (from the previous step) following the procedure described for Example 144. ^{1}H NMR (Acetone- d_6): δ 7.47 (s, 1H), 7.41 (s, 1H), 7.09 (d, 1H), 6.21 (s, 1H), 6.18 (d, 1H), 5.82 (d, 2H), 5.52 (d, 2H), 2.66 (t, 2H), 1.99 (t, 2H), 1.77 (t, 2H), 1.28 (s, 3H), 1.17 (t, 2H), 0.70-0.79 (m, 2H). LRMS [M+H] = 416.2.

Example 160

4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)butanoic acid



[000762] *Step 1: methyl 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)butanoate*

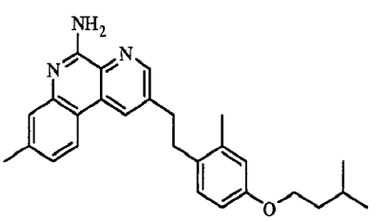
Methyl 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)butanoate was prepared following the same procedure described for the preparation of Example 158, but using 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol (from Example 50).

[000763] *Step 2: 4-(4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)butanoic acid*

4-(4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)butanoic acid was prepared from methyl 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)butanoate (from the previous step) following the procedure described for Example 144. ^{1}H NMR (Acetone- d_6): δ 8.38 (s, 1H), 8.24 (s, 1H), 7.90 (d, 1H), 6.90 (s, 1H), 6.68 (d, 1H), 6.54-6.63 (m, 2H), 6.27 (d, 1H), 6.20 (d, 1H), 3.40 (t, 2H), 2.62 (t, 2H), 2.47 (t, 2H), 1.99 (s, 3H), 1.80 (s, 2H), 1.45 (t, 2H), 1.27-1.39 (m, 2H). LRMS [M+H] = 430.2.

Example 161

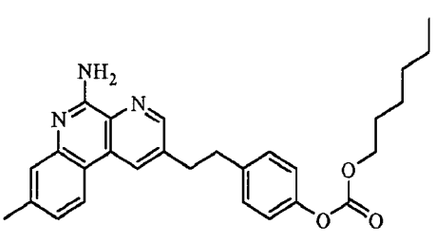
2-(4-(isopentyloxy)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



[000764] 2-(4-(Isopentyloxy)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol (from Example 50) following the procedure described for Example 136, but using 1-bromo-3-methylbutane. ^{1}H NMR (Acetone- d_6): δ 8.75 (s, 1H), 8.72 (s, 1H), 8.29 (d, 1H), 7.43 (s, 1H), 7.17 (D, 1H), 7.10 (d, 1H), 6.76 (d, 1H), 6.68(d, 1H), 6.56 (br, 2H), 4.00 (t, 2H), 3.17 (t, 2H), 3.07 (t, 2H), 2.48 (s, 3H), 1.76-1.91 (m, 1H), 1.60-1.71 (m, 2H), 0.96 (s, 6H). LRMS [M+H] = 414.2.

Example 162

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl hexyl carbonate

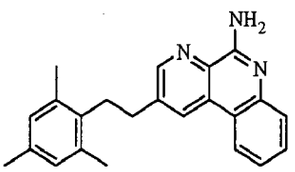


[000765] 4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl hexyl carbonate was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol (from Example

170) following the procedures described for Example 138, but using hexyl carbonochloridate. LRMS [M+H] = 458.2.

Example 163

2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine



Step 1: 2-(mesitylethynyl)benzo[f][1,7]naphthyridin-5-amine

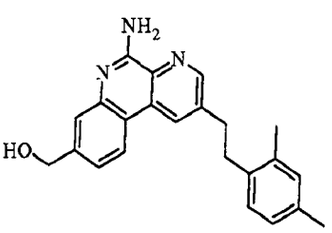
[000766] 2-(Mesitylethynyl)benzo[f][1,7]naphthyridin-5-amine was prepared from 3-chloro-5-(mesitylethynyl)picolinonitrile (Example 77 / Step 1) and *tert*-butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (commercially available) following the procedures described for Example 45 / Step 1.

Step 2: 2-(2,4,6-Trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine

[000767] 2-(2,4,6-Trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine was prepared from 2-(mesitylethynyl)benzo[f][1,7]naphthyridin-5-amine (from the previous step) following the procedures described for Example 45 / Step 2 to 3. ^{1}H NMR (Acetone- d_6): δ 8.80 (s, 2H), 8.38 (d, 1H), 7.60 (d, 2H), 7.54 (d, 2H), 7.31 (t, 1H), 6.84 (s, 2H), 6.61 (br, 2H), 3.08 (s, 2H), 2.30 (s, 6H), 2.23 (s, 3H). LRMS [M+H] = 342.2.

Example 164

(5-amino-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol



Step 1: methyl 5-amino-2-((2,4-dimethylphenyl)ethynyl)benzo[f][1,7]naphthyridine-8-carboxylate

[000768] Methyl 5-amino-2-((2,4-dimethylphenyl)ethynyl)benzo[f][1,7] naphthyridine-8-carboxylate was prepared from 3-chloro-5-((2,4-d methylphenyl) ethynyl)picolinonitrile (from Example 47 / Step 3) and 2-(*tert*-butoxycarbonylamino)-4-(methoxycarbonyl) phenylboronic acid (from Example 85 / Step1) following the procedures described in Example 95 / step 1.

Step 2: methyl 5-amino-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridine-8-carboxylate

[000769] Methyl 5-amino-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridine-8-carboxylate

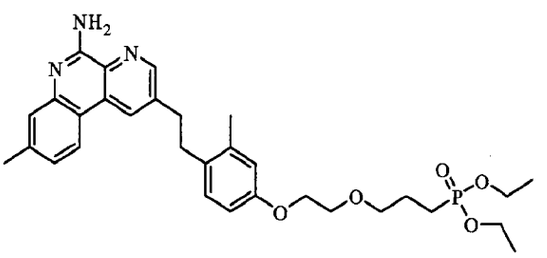
was prepared from methyl 5-amino-2-((2,4-dimethylphenyl)ethynyl) benzo[f][1,7]naphthyridine-8-carboxylate (from the previous step) following the procedures described in Example 44 / Step 5.

Step 3: (5-amino-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol

[000770] (5-Amino-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol was prepared from methyl 5-amino-2-(2,4-dimethylphenethyl)benzo[f][1,7] naphthyridine-8-carboxylate (from the previous step) following the procedures described in Example 95 / Step 2. ^{1}H NMR (Acetone- d_6): δ 8.79 (s, 1H), 8.73 (s, 1H), 8.35 (d, 1H), 7.61 (s, 1H), 7.34 (d, 1H), 7.08 (d, 1H), 6.97 (s, 1H), 6.91 (d, 1H), 6.51 (br. 2H), 4.77 (s, 2H), 3.16-3.20 (m, 2H), 3.04-3.10 (m, 2H), 2.28 (s, 3H), 2.25 (s, 3H). LRMS [M+H] = 358.2.

Example 165

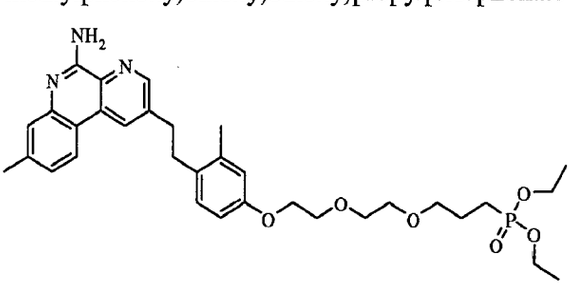
diethyl 3-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)propylphosphonate



[000771] Diethyl 3-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)propylphosphonate was prepared following the procedure described for Example 139, but using 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol (from Example 156) and diethyl 3-(2-bromoethoxy)propylphosphonate. LRMS [M+H] = 566.3.

Example 166

diethyl 3-(2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethoxy)propylphosphonate

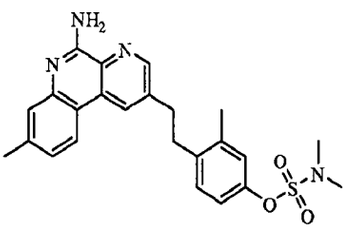


[000772] Diethyl 3-(2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethoxy)propylphosphonate was prepared from following the procedure

described for Example 139, but using 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol (from Example148) and diethyl 3-(2-(2-bromoethoxy)ethoxy)propylphosphonate. ^{1}H NMR (Acetone- d_6): δ 8.75 (s, 1H), 8.70 (s, 1H), 8.26 (d, 1H), 7.42 (s, 1H), 7.16 (d, 1H), 7.09 (d, 1H), 6.77 (s, 1H), 6.71 (d, 1H), 6.58 (br, 2H), 3.95-4.11 (m, 6H), 3.76-3.80 (m, 2H), 3.63-3.67 (m, 2H), 3.55-3.58 (m, 2H), 3.57-3.51 (m, 2H), 3.14-3.18 (m, 2H), 3.04-3.05 (m, 2H), 2.46 (s, 3H), 2.29 (s, 3H), 1.71-1.87 (m, 4H), 1.22-1.29 (m, 8H). LRMS [M+H] = 610.3.

Example 167

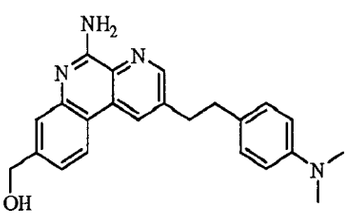
4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl dimethylsulfamate



[000773] 4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl dimethylsulfamate was prepared from 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol (from Example 50) following the procedure described for Example 138, but using dimethylsulfamoyl chloride. ^{1}H NMR (Acetone- d_6): δ 8.79 (s, 1H), 8.72 (s, 1H), 8.28 (d, 1H), 7.42 (s, 1H), 7.27 (d, 1H), 7.17 (s, 1H), 7.14 (t, 1H), 7.05-7.10 (d, 1H), 3.19-3.25 (m, 2H), 3.11-3.17 (m, 2H), 2.92 (s, 6H), 2.46 (s, 3H), 2.37 (s, 3H). LRMS [M+H] = 451.2.

Example 168

(5-amino-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol

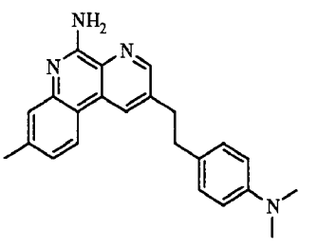


[000774] (5-Amino-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol was prepared from *tert*-butyl 5-((*tert*-butyldimethylsilyloxy)methyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (from Example 99 / step 1) and 4-ethynyl-N,N-dimethylaniline (commercially available) following the procedures described in Example 45 / Step 1 to 4 followed by deprotection of TBS group as in Example 99 / Step 3. ^{1}H NMR (Acetone- d_6): δ 8.78 (s, 1H), 8.73 (s, 1H), 8.35 (d, 1H), 7.61 (s, 1H), 7.31-7.35 (d, 1H), 7.08 (d, 1H), 6.68 (d, 2H), 6.50 (br, 2H), 4.78

(s, 2H), 4.34 (s, 1H), 3.16-3.20 (m, 2H), 3.03-3.10 (m, 2H), 2.83 (s, 3H), 2.80 (s, 3H). LRMS [M+H] = 373.2.

Example 169

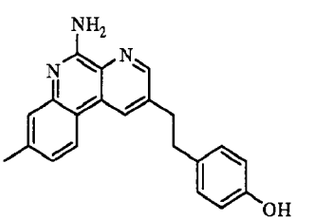
2-(4-(dimethylamino)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



[000775] 2-(4-(Dimethylamino)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared following the procedures described for Example 45 / Steps 1 to 3, but using 4-ethynyl-*N,N*-dimethylaniline in step 1. ^{1}H NMR (Acetone- d_6) Free base: δ 8.60 (s, 1H), 8.55 (s, 1H), 8.15 (d, 1H), 7.28 (s, 1H), 7.03 (d, 1H), 6.96 (d, 2H), 6.56 (d, 2H), 6.55 (br s, 2H), 3.05 (t, 2H), 2.88 (t, 2H), 2.75 (s, 6H), 2.33 (s, 3H). LRMS [M+H] = 357.2

Example 170

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol



Step 1: 2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

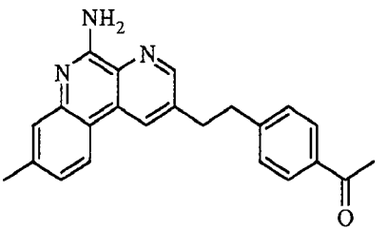
[000776] 2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared following the procedures described for Example 79 / Steps 1 to 3, but using 1-ethynyl-4-methoxybenzene in Step 1.

Step 2: 4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol

[000777] 4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol was prepared from 2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine (from the previous step) following the procedure described for Example 50. ^{1}H NMR (Methanol- d_4): δ 8.59

Example 171

1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone



Step 1: 5-((4-acetylphenyl)ethynyl)-3-chloropicolinonitrile

[000778] To a solution of 1-(4-ethynylphenyl)ethanone (commercially available) (1 eq) 3,5-dichloropicolinonitrile (1 eq), dichlorobis(triphenylphosphine)-palladium (II) (20 mol%), copper iodide (10 mol%) and DMF: Triethylamine (10:1) (0.13 M) was stirred at ambient temperature overnight. The reaction mixture was then diluted with ethyl acetate and sodium bi-carbonate solution. The two phases were separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-100% ethyl acetate in hexane and 5-((4-acetylphenyl)ethynyl)-3-chloropicolinonitrile was isolated as a yellow solid

Step 2: 5-(4-acetylphenethyl)-3-chloropicolinonitrile

[000779] To a solution of 5-((4-acetylphenyl)ethynyl)-3-chloropicolinonitrile (from the previous step) (1 eq) in ethanol (0.1 M) was added Platinum Oxide (30 mol%). Hydrogen gas was introduced via a balloon, and the reaction was stirred for 0.5 hour. The mixture was filtered through a pad of celite, washing with dichloromethane. The filtrate was concentrated *en vaccuo* and purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-100% ethyl acetate in hexane to give 5-(4-acetylphenethyl)-3-chloropicolinonitrile as an off-white solid.

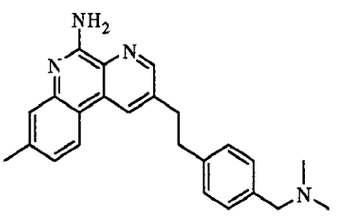
Step 3: 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone

[000780] To a solution of *5-(4-acetylphenethyl)-3-chloropicolinonitrile* (from the previous step) (1 eq) and tert-butyl 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (10 mol%), and 2N aqueous sodium carbonate solution (2.0 eq.) in toluene/ethanol (1:1, 0.09 M) was heated under microwave condition using a BIOTAGE INITIATOR 2.0 at 150 ^{0}C for 20 minutes. After cooling to ambient temperature, the reaction mixture was diluted with ethanol/water. The insoluble solids were filtered off, and the filtrate was concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone as a yellow solid.

^{1}H NMR (Methanol- d_4) TFA Salt: δ 8.69 (d, 2H), 8.30 (d, 1H), 7.80 (d, 2H), 7.3 8 (s, 1H), 7.36(d, 1H), 7.28 (d, 2H), 3.25 (t, 2H), 3.13 (t, 2H), 2.47 (s, 3H), 2.45 (s, 3H).
LRMS [M+H] = 356.2

Example 172

2-(4-((dimethylamino)methyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



Step 1: 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzaldehyde

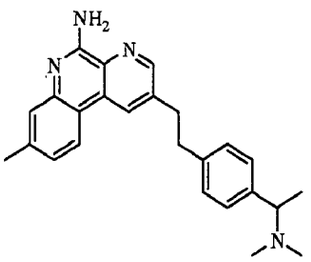
[000781] 4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzaldehyde was prepared from 4-ethynylbenzaldehyde (commercially available) following the procedures described for Example 171 / Steps 1 to 3.

Step 2:2-(4-((dimethylamino)methyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000782] A solution of 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzaldehyde (from the previous step) (1 eq), sodium acetate (3.5 eq) and N, N'-dimethyl amine hydrochloride (3.5 eq) dissolved in 1-2, dichloroethane(0.04 M) was heated at 80 ^{0}C for 2 hours in a sealed vial. After cooling to ambient temperature, the reaction mixture was further cooled down to 0 ^{0}C and sodium tri-acetoxy borohydride (1.25 eq) was added. The reaction mixture was stirred at room temperature for one hour. The mixture was diluted with ethyl acetate and water. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by preparative HPLC using 10-90% acetonitrile/water as the gradient and 2-(4-((dimethylamino)methyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was isolated as a off-white powder as a TFA salt. ^{1}H NMR (Methanol- d_4) TFA Salt: δ 8.83 (s, 1H), 8.81 (s, 1H), 8.41 (d, 1H), 7.52 (s, 1H), 7.45 (d, 1H), 7.43 (s, 1H), 7.40 (m, 3H), 4.29 (s, 2H), 3.30-3.24 (m, 4H), 2.79 (s, 6H), 2.60 (s, 3H). LRMS [M+H] = 371.2

Example 173

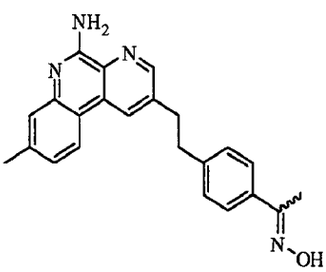
2-(4-(1-(dimethylamino)ethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



[000783] 2-(4-(1-(Dimethylamino)ethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared from 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone (from Example 171) following the procedures described for Example 172 / Step 2. ^{1}H NMR (Methanol- d_4) TFA Salt: δ 8.84 (s, 1H), 8.79 (s, 1H), 8.40 (d, 1H), 7.52 (s, 1H), 7.44 -7.46 (m, 2H), 7.38-7.42 (m, 3H), 4.45 (m, 1H), 3.31 (t, 2H), 3.19 (t, 2H), 2.83 (s, 3H), 2.66 (s, 3H), 2.56 (s, 3H), 1.70 (d, 3H). LRMS [M+H] = 385.2

Example 174

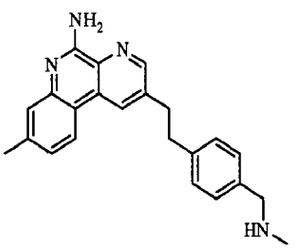
1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone oxime



[000784] A solution of 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone (from Example 171) (1eq), hydroxylamine hydrochloride (2eq) and 1 drop of HOAc, dissolved in absolute ethanol (0.028M) was stirred at room temperature for 1.5 hours. The mixture was diluted with ethyl acetate and water. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 10-80% ethyl acetate in hexane to give 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone oxime as a white solid. ^{1}H NMR (Methanol- d_4): δ 8.56 (s, 1H), 8.52 (s, 1H), 8.12 (d, 1H), 7.45 (d, 2H), 7.31 (s, 1H), 7.12 (m, 3H), 4.51 (s, OH), 3.15 (t, 2H), 3.01 (t, 2H), 2.39 (s, 3H), 2.09 (s, 3H). LRMS [M+H] = 371.2

Example 175

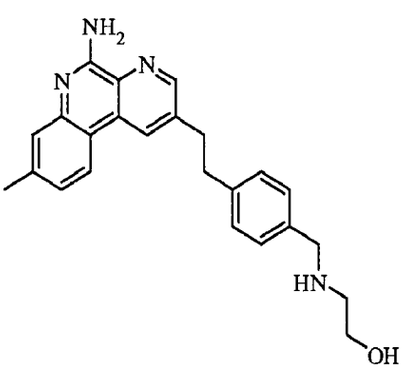
8-methyl-2-(4-((methylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine



[000785] 8-Methyl-2-(4-((methylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine was prepared from 4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzaldehyde (from Example 172 / Step 1) and methylamine following the procedures described for Example 172, step 2. ^{1}H NMR (Acetone- d_6) TFA Salt: δ 8.95 (s, 1H), 8.88 (s, 1H), 8.43 (d, 1H), 7.58 (s, 1H), 7.54 (d, 2H), 7.42 (d, 1H), 7.37 (d, 2H), 4.30 (s, 2H), 3.32-3.37 (m, 4H), 2.75 (s, 3H), 2.55 (s, 3H). LRMS [M+H] = 357.2

Example 176

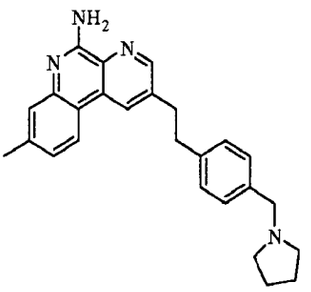
(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzylamino)ethanol



[000786] A solution of 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzaldehyde (from Example 172 / Step 1) (1eq), ethanol amine (8eq) and 1 drop of HOAc, dissolved in absolute ethanol (0.018M) was stirred at 80 ^{0} C for 2 hours. The mixture was cooled down to 0 ^{0}C and $NaBH_4$ (3.5 eq) was added and the reaction mixture was stirred for another one hour at room temperature. The mixture was diluted with ethyl acetate and water. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by Preparative HPLC on a 19x50 mm ATLANTIS® 10 micron C18 (Waters Corp.) system using 10-90% Acetonitrile (0.035% TFA) in Water (0.05% TFA) to give a light yellow solid as a TFA salt. ^{1}H NMR (Acetone- d_6) TFA Salt: δ 8.82 (s, 1H), 8.75 (s, 1H), 8.30 (d, 1H), 7.44 (m, 3H), 7.28(d, 1H), 7.21 (d, 2H), 4.22 (s, 2H), 3.72 (t, 2H), 3.22 (t, 2H), 3.09 (m, 2H), 3.07 (t, 2H), 3.01 (bs, OH), 2.41 (s, 3H), LRMS [M+H] = 387.2

Example 177

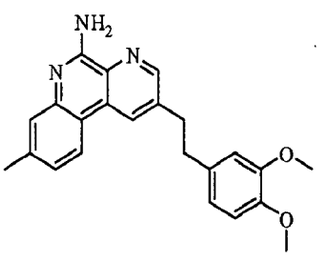
8-methyl-2-(4-(pyrrolidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine



[000787] 8-Methyl-2-(4-(pyrrolidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine was prepared from 4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzaldehyde (from Example 172 / Step 1) and pyrrolidine following the procedures described for Example 172, step 2. ^{1}H NMR (Acetone- d_6) TFA Salt: δ 8.88 (s, 1H), 8.82 (s, 1H), 8.82 (s, 1H), 8.43 (d, 1H), 8.38 (d, 1H), 7.58 (s, 1H), 7.51 (m, 1H), 7.33 (d, 2H), 4.16 (s, 2H), 3.32-3.38 (m, 4H), 2.55 (s, 3H), 2.20-2.32 (m, 4H), 1.90-1.99 (m, 4H). LRMS [M+H] = 397.2

Example 178

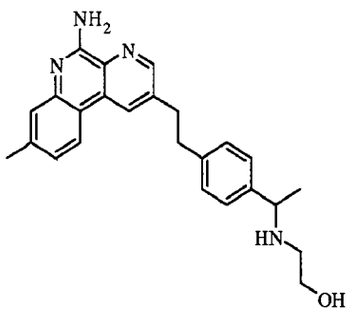
2-(3,4-dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



[000788] 2-(3,4-Dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine was prepared from 4-ethynyl-1,2-dimethoxybenzene (commercially available) following the procedures described for Example 45 / Steps 1 to 3. ^{1}H NMR (Acetone- d_6): δ 8.64 (s, 1H), 8.56 (s, 1H), 8.14 (d, 1H), 7.29 (s, 1H), 7.03 (d, 1H), 6.77 (s, 1H), 6.71 (s, 1H), 6.62 (d, 1H), 6.45 (bs, 2H), 3.62 (s, 6H), 3.12 (t, 2H), 2.94 (t, 2H), 2.33 (s, 3H). LRMS [M+H] = 374.2

Example 179

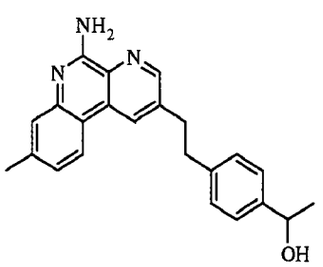
2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)ethanol



[000789] 2-(1-(4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)ethanol (from Example 171) was prepared from 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone and ethanol amine (commercially available) following the procedures described for Example 176. ^{1}H NMR (Acetone- d_6) of TFA Salt: δ 8.78 (d, 1H), 8.29 (d, 1H), 7.83 (s, 1H), 7.45 (m, 3H), 7.28 (m, 3H), 4.22 (m, 1H), 3.52 (m, 2H), 3.23 (t, 2H), 3.09 (t, 2H), 2.85 (m, 1H), 2.65 (m, 1H), 2.41 (s, 3H), 1.61 (d, 3H). LRMS [M+H] = 401.2

Example 180

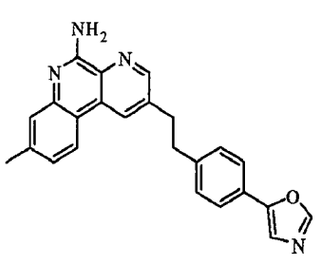
1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanol



[000790] 1-(4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanol (from Example 171) was isolated as a side product during the reductive amination as shown in Example 173. ^{1}H NMR (Acetone- d_6) of TFA Salt: δ 8.90 (s, 1H), 8.88 (s, 1H), 8.42 (d, 1H), 7.57 (s, 1H), 7.43 (d, 1H), 7.33 (d, 2H), 7.26 (d, 2H), 4.82 (q, 1H), 3.32 (t, 2H), 3.17 (t, 2H), 3.01 2.55 (s, 3H), 1.41 (s, 3H). LRMS [M+H] = 358.2

Example 181

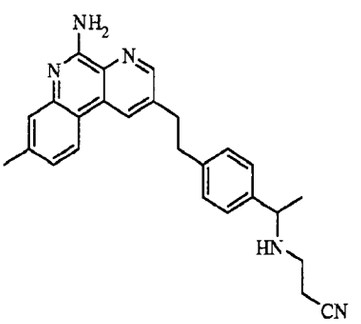
8-methyl-2-(4-(oxazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine



[000791] 8-Methyl-2-(4-(oxazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine was prepared from 5-(4-ethynylphenyl)oxazole (commercially available) following the procedures described for Example 45 / Steps 1 to 3. ^{1}H NMR (Acetone- d_6) of TFA Salt: 8.69 (s, 1H), 8.59 (s, 1H), 8.16 (d, 1H), 8.04 (s, 1H), 7.55 (m, 2H), 7.38 (s, 1H), 7.28 (m, 2H), 7.01 (m, 2H), 3.16 (t, 2H), 3.07 (t, 2H), 2.33 (s, 3H). LRMS [M+H] = 381.2

Example 182

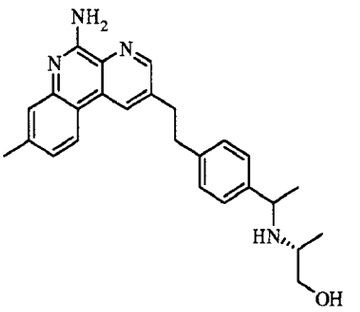
3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propanenitrile



[000792] A solution of 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone (from Example 171) (1 eq), 3-aminopropane nitrile (commercially available) (2.5 eq) dissolved in absolute ethanol (0.014M) was stirred at 80 ^{0} C for 2 hours. The mixture was cooled to 0 ^{0}C and $NaCNBH_3$ (2 eq) was added and the reaction mixture was stirred for another hour at room temperature. The mixture was diluted with ethyl acetate and ammonium chloride. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by Preparative HPLC on a 19x50 mm ATLANTIS® 10 micron C18 (Waters Corp.) system using 10-90% Acetonitrile (0.035% TFA) in Water (0.05% TFA) to give 3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propanenitrile as a light yellow solid as a TFA salt. ^{1}H NMR (Acetone-d_6): δ 8.60 (s, 1H), 8.59 (s, 1H), 8.11 (d, 1H), 7.29 (s, 1H), 7.16 (d, 2H), 7.09 (d, 2H), 7.03 (d, 1H), 6.43 (bs, 2H), 3.65 (m, 1H), 3.12 (t, 2H), 2.99 (t, 2H), 2.56 (m, 2H), 2.35 (m, 2H), 2.32 (s, 3H), 1.16 (d, 3H). LRMS [M+H] = 410.2

Example 183

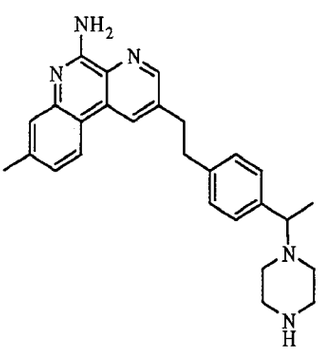
(2R)-2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propan-1-ol



[000793] (2R)-2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propan-1-ol was prepared from 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone (from Example 171) and (R)-2-aminopropan-1-ol (commercially available) following the procedures described for Example 182. ^{1}H NMR (Acetone- d_6) : δ: 8.94 (m, 2H), 8.45 (m, 1H), 7.64 (d, 2H), 7.59 (s, 1H), 7.55 (br s, 2H), 7.41 (m, 3H), 4.65 (m, 1H), 3.81 (m, 1H), 3.35 (t, 2H), 3.25 (t, 2H), 2.56 (s, 3H), 1.73 (m, 3H), 1.29 (d, 3H), 1.23 (d, 3H). LRMS [M+H] = 415.2

Example 184

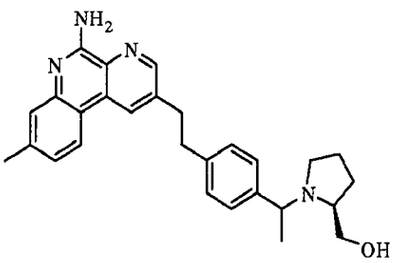
8-methyl-2-(4-(1-(piperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine



[000794] 8-Methyl-2-(4-(1-(piperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine was prepared from 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone (from Example 171) and piperazine (commercially available) following the procedures described for Example 182. ^{1}H NMR (Methanol- d_4) TFA Salt: δ 8.83 (s, 1H), 8.75 (s, 1H), 8.39 (d, 1H), 7.51 (s, 1H), 7.46 (d, 1H), 7.26 (m, 4H), 3.62 (m, 1H), 3.25 (t, 2H), 3.12 (t, 2H), 2.80 (m, 4H), 2.69 (m, 4H), 2.56 (s, 3H), 1.42 (d, 3H). LRMS [M+H] = 426.2

Example 185

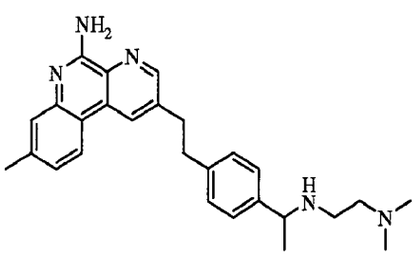
((2S)-1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidin-2-yl)methanol



[000795] ((2S)-1-(1-(4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidin-2-yl)methanol was prepared from 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone (from Example 171) and (S)-pyrrolidin-2-ylmethanol (commercially available) following the procedures described for Example 182. ^{1}H NMR (Acetone- d_6) TFA Salt: δ 8.83 (s, 1H), 8.80 (s, 1H), 8.43 (d, 1H), 7.36-7.53 (m, 6H), 4.68 (m, 1H), 3.69 (m, 2H), 3.19-3.21 (m, 4H), 2.55 (m, 4H), 1.75-1.78 (m, 6H), 1.74 (d, 3H). LRMS [M+H] = 441.2

Example 186

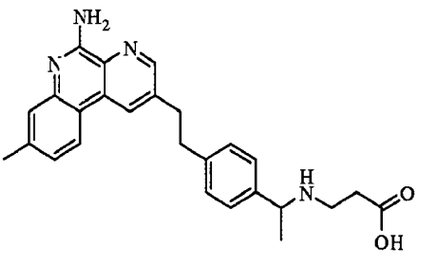
N^1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^2,N^2-dimethylethane-1,2-diamine



[000796] N^1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^2,N^2-dimethylethane-1,2-diamine was prepared from 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone (from Example 171) and N^1,N^1-dimethylethane-1,2-diamine (commercially available) following the procedures described for Example 182. ^{1}H NMR (Acetone- d_6) TFA Salt: δ 8.85 (m, 2H), 8.43 (d, 1H), 7.52 (s, 1H), 7.48 (m, 2H), 7.40 (m, 2H), 6.69 (m, 1H), 4.39 (m, 1H), 3.42 (m, 2H), 3.18-3.25 (m, 6H), 2.87 (s, 6H), 2.56 (s, 3H), 1.69 (d, 3H). LRMS [M+H] = 428.2

Example 187

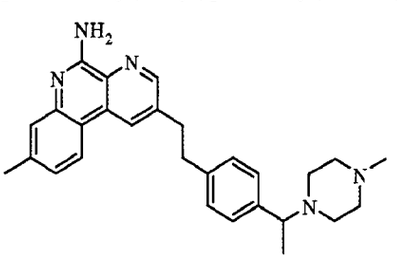
3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propanoic acid



[000797] A solution of 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone (from Example 171) (1 eq), 3-aminopropanoic acid (commercially available) (5 eq), triethylamine (3 eq) dissolved in absolute ethanol (0.042M) was stirred at 50 ^{0} C for 3 hours. The mixture was cooled to 0 ^{0}C and $NaCNBH_3$ (1 eq) was added and the reaction mixture was stirred for another six hours at room temperature. Then another equivalent of $NaCNBH_3$ was added and the reaction mixture was stirred at 50 ^{0}C for another hour. After cooling to ambient temperature the reaction mixture was diluted with ethyl acetate and saturated ammonium chloride. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by Preparative HPLC on a 19x50 mm ATLANTIS® 10 micron C18 (Waters Corp.) system using 10-90% Acetonitrile (0.035% TFA) in Water (0.05% TFA) to give 3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propanoic acid a white solid as a TFA salt. ^{1}H NMR (Methanol- d_4) TFA Salt: δ 8.74 (s, 1H), 8.42 (d, 1H), 7.66 (m, 2H), 7.50 (m, 1H), 7.31 (d, 2H), 7.23 (m, 2H), 4.24 (m, 1H), 3.21 (t, 2H), 3.14 (t, 2H), 2.75-3.10 (m, 2H), 2.51 (t, 2H), 2.10 (s, 3H), 1.55 (d, 3H). LRMS [M+H] = 429.2

Example 188

8-methyl-2-(4-(1-(4-methylpiperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine

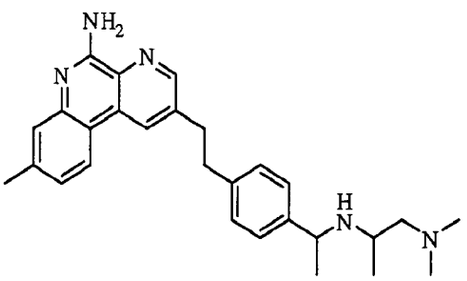


[000798] 8-Methyl-2-(4-(1-(4-methylpiperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine was prepared from 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone (from Example 171) and 1-methylpiperazine (commercially available) following the procedures described for Example 182. ^{1}H NMR (Acetone- d_6) TFA Salt: δ 8.84 (s,

1H), 8.80 (s, 1H), 8.41 (d, 1H), 7.52 (s, 1H), 7.42-7.46 (m, 3H), 7.36-7.38 (m, 2H), 3.53 (m, 1H), 3.18 (m, 2H), 3.12 (m, 2H), 2.92 (s, 2H), 2.66 (s, 2H), 2.56 (s, 2H), 2.16 (s, 3H), 1.99 (m, 2H), 1.69 (d, 3H), 1.30 (s, 3H). LRMS [M+H] = 440.2

Example 189

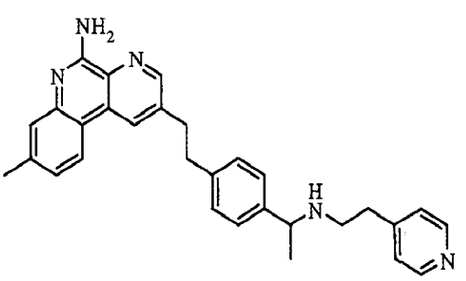
N^2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^1,N^1-dimethylpropane-1,2-diamine



[000799] N^2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^1,N^1-dimethylpropane-1,2-diamine was prepared from 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone (from Example 171) and N^1,N^1-dimethylpropane-1,2-diamine (commercially available) following the procedures described for Example 182. ^{1}H NMR (Acetone- d_6) TFA Salt: δ 8.83 (m, 2H), 8.40 (d, 1H), 7.46-7.51 (m, 3H), 7.43 (m, 1H), 7.37 (d, 2H), 4.54 (m, 1H), 3.74 (m, 1H), 3.19 (m, 4H), 2.90 (s, 3H), 2.77 (s, 3H), 2.55 (s, 3H), 2.41 (d, 2H), 1.66 (d, 3H), 1.39 (d, 3H). LRMS [M+H] = 442.2

Example 190

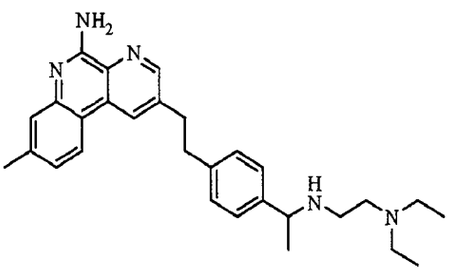
8-methyl-2-(4-(1-(2-(pyridin-4-yl)ethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine



[000800] 8-Methyl-2-(4-(1-(2-(pyridin-4-yl)ethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine was prepared from 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone (from Example 171) and 2-(pyridin-4-yl)ethanamine (commercially available) following the procedures described for Example 182. ^{1}H NMR (Acetone- d_6) TFA Salt: δ 8.94 (m, 2H), 8.92 (d, 2H), 8.73 (s, 1H), 8.43 (d, 1H), 7.60 (m, 2H), 7.40 (m, 2H), 7.16-7.26 (m, 3H), 4.55 (m, 1H), 3.55 (m, 4H), 2.56 (m, 4H), 2.12 (s, 3H), 1.73 (d, 3H) LRMS [M+H] = 462.2

Example 191

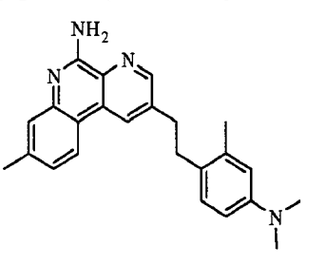
N^1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^2,N^2-diethylethane-1,2-diamine



[000801] N^1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^2,N^2-diethylethane-1,2-diamine was prepared from 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone (from Example 171) and N^1,N^1-diethylethane-1,2-diamine (commercially available) following the procedures described for Example 182. ^{1}H NMR (Acetone- d_6) TFA Salt: δ: 8.81 (s, 1H), 8.75 (s, 1H), 8.23 (d, 1H), 7.60 (d, 2H), 7.39 (d, 2H), 7.28 (m, 2H), 4.51 (m, 1H), 3.82 (m, 1H), 3.62 (m, 1H), 3.34 (m, 4H), 3.20 (t, 2H), 2.46 (s, 3H), 2.10 (m, 4H), 1.74 (d, 3H), 1.34 (t, 6H). LRMS [M+H] = 456.2

Example 192

2-(4-(dimethylamino)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



Step 1: 4-iodo-N,N,3-trimethylaniline

[000802] To a solution of 4-iodo-3-methylaniline (commercially available) (1 eq), $NaHCO_3$ (2.5 eq), and iodomethane (2.5 eq), in DMF ((0.2M) was stirred at ambient temperature overnight. The reaction mixture was then diluted with ethyl acetate and water. The two phases were separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane and 4-iodo-N,N,3-trimethylaniline was isolated as a yellow solid.

Step 2: Syntheswas of: N,N,3-trimethyl-4-((trimethylsilyl)ethynyl)aniline

[000803] To a solution of 4-iodo-*N,N*-3-trimethylaniline (from the previous step) (1 eq), ethynyltrimethylsilane (1.5 eq), dichlorobis(triphenylphosphine)-palladium (II) (20 mol%), copper iodide (20 mol%) and triethylamine (0.4 M) was stirred at ambient temperature overnight. The reaction mixture was then diluted with ethyl acetate and ammonium chloride solution. The two phases were separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-100% ethyl acetate in hexane and N,N,3-trimethyl-4-((trimethylsilyl)ethynyl)aniline was isolated as a yellow solid.

Step3: 4-ethynyl-N,N,3-trimethylaniline

[000804] To a solution of *N,N*-3-trimethyl-4-((trimethylsilyl)ethynyl)aniline (from the previous step) (1 eq), K_2CO_3 (2.5 eq), in MeOH ((0.15M) was stirred at ambient temperature for six hours. The solids were filtered out, and the liquid was concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane and 4-ethynyl-*N,N*-3-trimethylaniline was isolated as a yellow solid.

Step 4: 3-chloro-5-((4-(dimethylamino)-2-methylphenyl)ethynyl) picolinonitrile

[000805] To a solution of 4-ethynyl-*N,N*-3-trimethylaniline (from the previous step) (1 eq) 3,5-dichloropicolinonitrile (1.2 eq), dichlorobis(triphenylphosphine)-palladium (II) (10 mol%), copper iodide (10 mol%) and DMF: triethylamine (0.28 M) was stirred at ambient temperature overnight. The reaction mixture was then diluted with ethyl acetate and ammonium chloride solution. The two phases were separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *en vaccuo*. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-100% ethyl acetate in hexane and 3-chloro-5-((4-(dimethylamino)-2-methylphenyl)ethynyl) picolinonitrile was isolated as a off-yellow solid.

Step 5: 2-((4-(dimethylamino)-2-methylphenyl)ethynyl)-8-methylbenzo[f] [1,7] naphthyridin-5-amine

[000806] A solution of tert-butyl 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (1.3 eq.) and 3-chloro-5-((4-(dimethylamino)-2-methylphenyl)ethynyl) picolinonitrile (from the previous step) (1.0 eq.), tetrakis(triphenyl-phosphine)palladium (10 mol%), and 2N aqueous sodium carbonate solution (2.0 eq.) in toluene/ethanol (2:1, 0.17 M) was stirred at 100°C overnight. After cooling to ambient temperature, the reaction mixture was diluted with

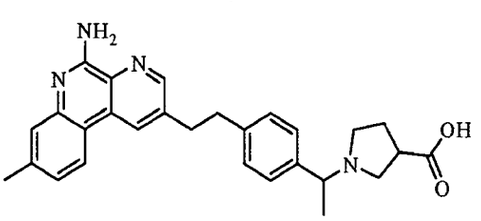
methanol. The insoluble solids were filtered off, and the filtrate was concentrated *en vaccuo* to obtain a crude residue. The crude material was purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give 2-((4-(dimethylamino)-2-methylphenyl)ethynyl)-8-methylbenzo[f] [1,7] naphthyridin-5-amine as a yellow solid.

Step 6: 2-(4-(dimethylamino)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000807] To a solution of 2-((4-(dimethylamino)-2-methylphenyl)ethynyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine (1 eq), (from the previous step) in ethyl acetate/ethanol(1:5, 0.035 M) was added 10% wt palladium on carbon (0.2 eq.). Hydrogen gas was introduced via a balloon, and the reaction was stirred for 3.5 hours. The mixture was filtered through a pad of celite, washing with dichloromethane. The filtrate was concentrated *en vaccuo* and purified by preparative HPLC on a 19x50 mm ATLANTIS® 10 micron C18 (Waters Corp.) system using 10-90% Acetonitrile (0.035% TFA) in Water (0.05% TFA) to give 2-(4-(dimethylamino)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine as a white solid as a TFA salt. ^{1}H NMR (Acetone- d_6) TFA Salt: δ 8.81 (s, 1H), 8.74 (s, 1H), 8.34 (d, 1H), 7.89 (s, 1H), 7.47 (m, 2H), 7.38 (m, 2H), 3.34 (s, 6H), 3.32 (t, 2H), 3.28 (t, 2H), 2.57 (s, 3H), 2.34 (s, 3H). LRMS [M+H] = 371.2

Example 193

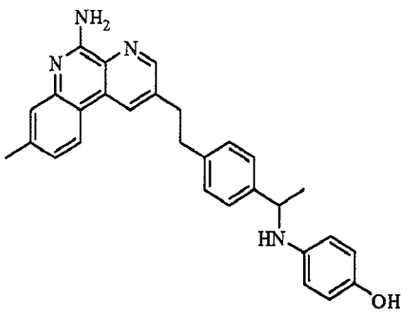
1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid



[000808] 1-(1-(4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid was prepared from 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone (from Example 171) and pyrrolidine-3-carboxylic acid (commercially available) following the procedures described for Example 187, except that in this case, acetic acid was used instead of triethylamine (30 %). ^{1}H NMR (Acetone- d_6) TFA Salt: δ 8.81 (s, 1H), 8.75 (s, 1H), 8.70 (s, 1H), 8.28 (d, 1H), 7.59 (d, 2H), 7.37 (m, 3H), 4.46 (m, 1H), 4.21 (m 1H), 3.45 (m, 2H), 3.32 (m, 2H), 3.21 (m, 2H), 3.17 (m, 2H), 2.27 (m, 2H), 2.07 (s, 3H) 1.77 (d, 3H). LRMS [M+H] = 455.2

Example 194

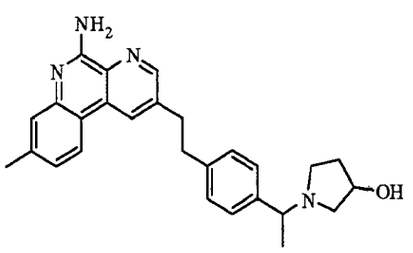
4-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)phenol



[000809] 4-(1-(4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)phenol was prepared from 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone (from Example 171) and 4-aminophenol following the procedures described for Example 187, except that in this case, acetic acid was used instead of triethylamine (28 %). ^{1}H NMR (Acetone- d_6) TFA Salt: δ 8.83 (s, 1H), 8.73 (s, 1H), 8.33 (d, 1H), 7.44 (s, 1H), 7.40 (d, 2H), 7.36 (d, 1H), 7.24 (d, 2H), 7.10 (d, 2H), 6.76 (d, 2H), 4.72 (m, 1H) 3.27 (t, 2H), 3.12 (t, 2H), 2.50 (s, 3H), 2.06 (d, 3H). LRMS [M+H] = 449.2

Example 195

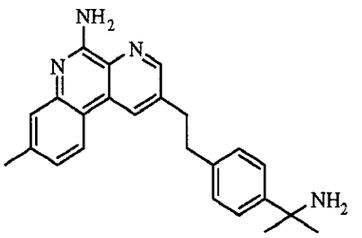
1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2 yl)ethyl)phenyl)ethyl)pyrrolidin-3-ol



[000810] 1-(1-(4-(2-(5-Amino-8-methylbenzo[f][1,7]naphthyridin-2 yl)ethyl)phenyl)ethyl)pyrrolidin-3-ol was prepared from 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone (from Example 171) and pyrrolidin-3-ol following the procedures described for Example 187, except that in this case, acetic acid was used instead of triethylamine (20 %). ^{1}H NMR (Acetone- d_6) TFA Salt: δ 8.83 (s, 1H), 8.76 (s, 1H), 8.72 (s, 1H), 8.29 (d, 1H), 7.57 (s, 1H), 7.42 (s, 1H), 7.33-7.38 (m, 3H), 4.41(m, 2H), 3.77 (m, 2H), 3.33 (t, 2H), 3.21 (t, 2H), 3.19 (m, 2H), 3.10 (m, 2H), 2.10 (s, 3H), 1.75 (d, 3H). LRMS [M+H] = 427.2

Example 196

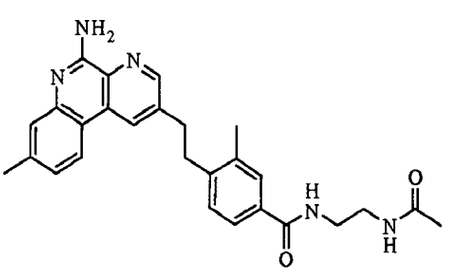
2-(4-(2-aminopropan-2-yl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine



[000811] To a solution of 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzonitrile (from Example 64, step 1) (1 eq), dissolved in dry THF (0.029M) was added very slowly methyl magnesium bromide (6 eq) and the reaction mixture was stirred at room temperature for half hour. Then was added to the reaction flask titanium tetra-isopropoxide (3 eq) over ten minutes. The reaction mixture was refluxed for 16 hours. After cooling to ambient temperature the reaction mixture was diluted with ethyl acetate and saturated ammonium chloride. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was purified by Preparative HPLC on a 19x50 mm ATLANTIS® 10 micron C18 (Waters Corp.) system using 10-90% Acetonitrile (0.035% TFA) in Water (0.05% TFA) to give 2-(4-(2-aminopropan-2-yl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine as a white solid of TFA salt. ^{1}H NMR (Methanol- d_4) TFA Salt δ: 9.01 (s, 2H), 8.92 (s, 1H), 8.42 (s, 1H), 7.65 (d, 2H), 7.56 (s, 1H), 7.39 (m, 2H), 3.19 (m, 4H), 2.54 (s, 3H), 1.82 (6H). LRMS [M+H] = 371.2.

Example 197

N-(2-acetamidoethyl)-4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide

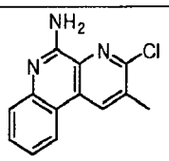
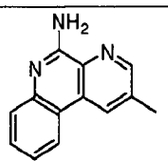
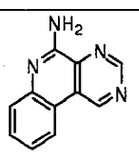
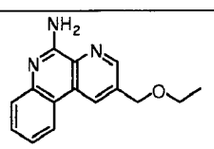
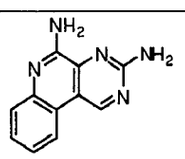
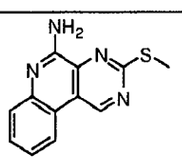
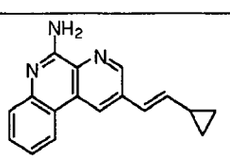


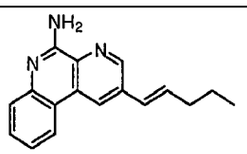
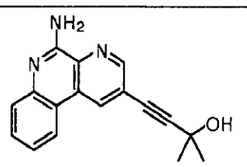
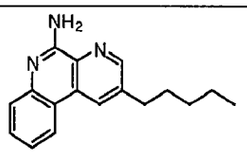
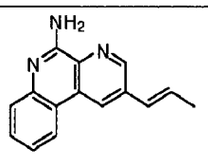
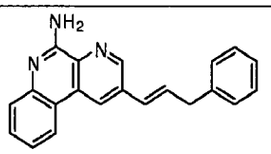
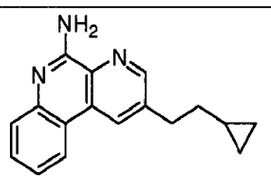
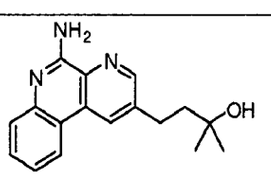
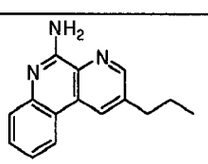
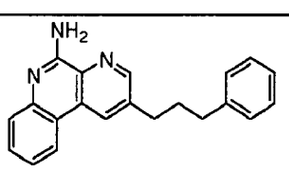
[000812] To a solution of 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoyl chloride (Example 116 / Step 2) and triethylamine (2.5 eq.) in ether (0.05 M) was added N-(2-aminoethyl)acetamide (5.0 eq.). The reaction mixture was stirred for overnight. Then the reaction mixture was diluted with ethyl acetate and water. The two phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *en vaccuo*. The crude material was

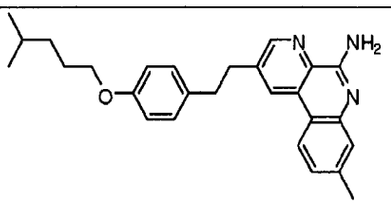
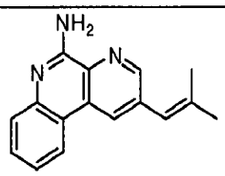
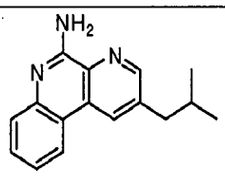
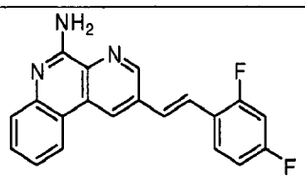
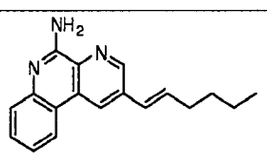
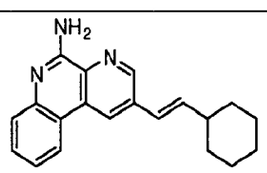
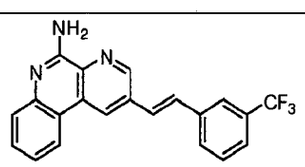
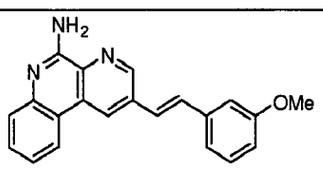
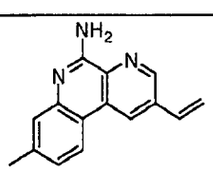
purified by flash chromatography on a COMBIFLASH® system (ISCO) using 0-80% ethyl acetate in hexane to give N-(2-acetamidoethyl)-4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.61 (s, 1H), 8.38 (s, 1H), 8.07 (d, 1H), 7.65 (s, 1H), 7.51-7.56 (m, 2H), 7.10-7.16 (m, 2H), 6.25 (br, 2H), 3.50-3.59 (m, 4H), 3.08-3.16 (m, 4H), 2.62 (s, 3H), 2.52 (s, 3H), 2.35(s, 3H). LRMS [M+H] = 455.2.

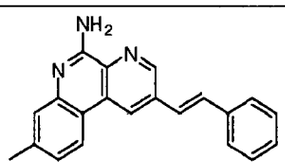
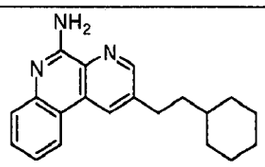
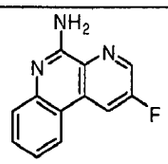
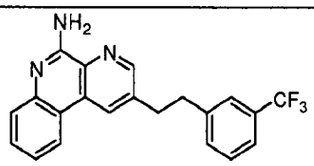
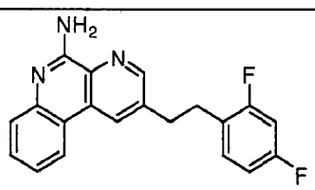
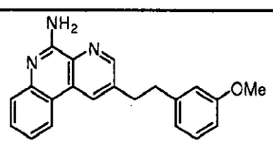
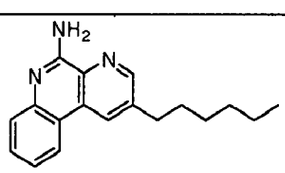
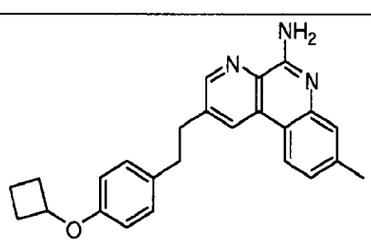
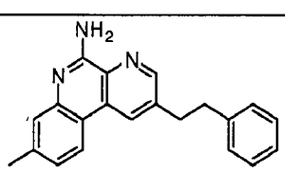
[000813] Additional representative compounds of Formula (I), prepared following the procedures described above, are set forth in Table 1.

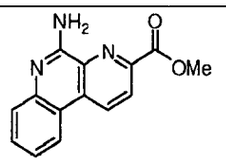
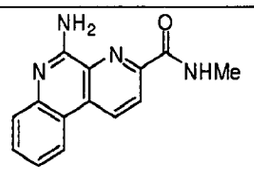
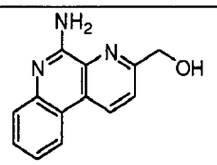
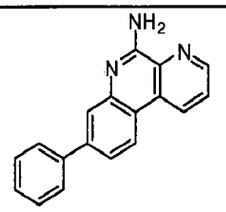
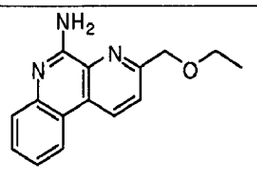
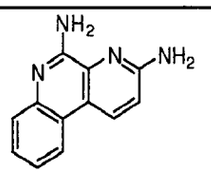
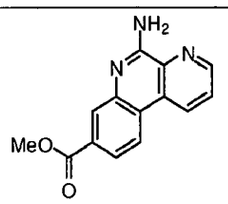
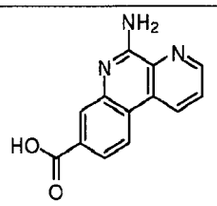
Table 1

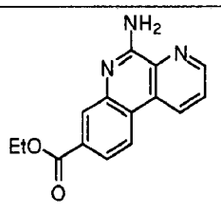
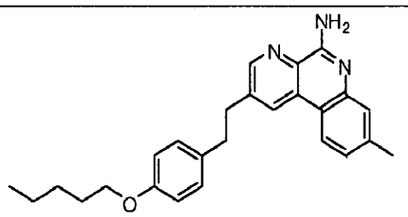
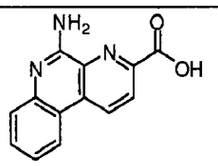
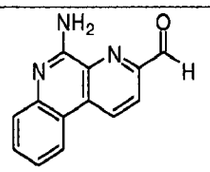
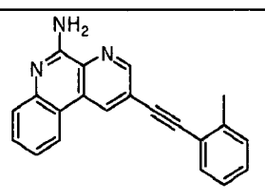
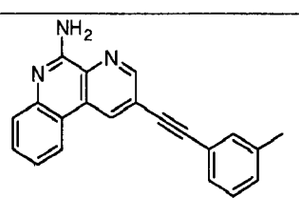
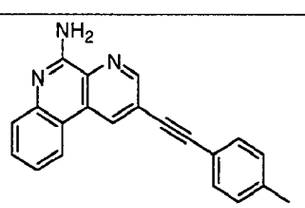
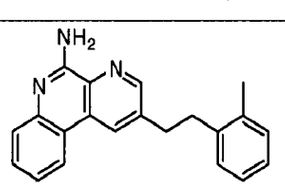
Compound Number	Structure	Physical Data MS (m/z) [M+H]
1		244.0
2		210.2
3		197.1
4		254.1
5		212.1
6		243.1
7		262.1

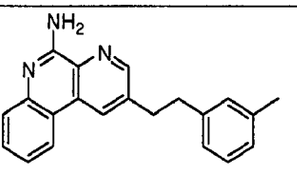
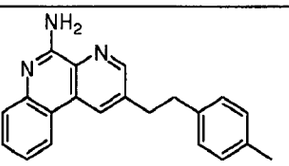
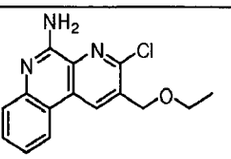
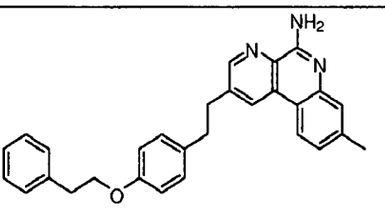
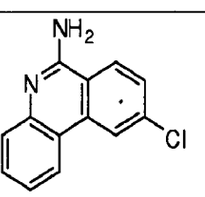
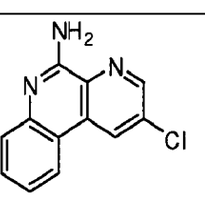
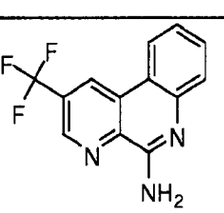
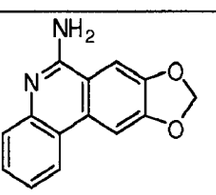
8		264.1
9		278.1
10		266.2
11		236.2
12		312.1
13		264.1
14		282.1
15		238.2
16		314.2

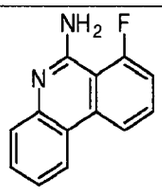
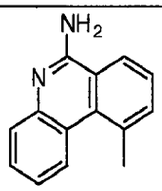
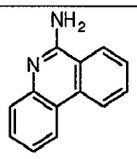
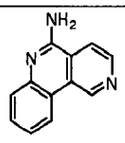
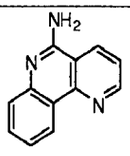
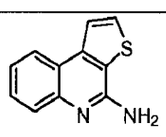
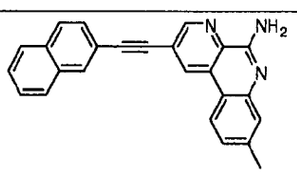
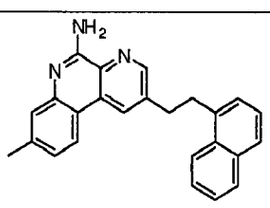
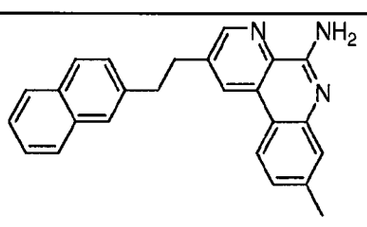
17		414.2
18		250.1
19		252.1
20		334.1
21		278.2
22		304.2
23		366.2
24		328.2
25		236.1

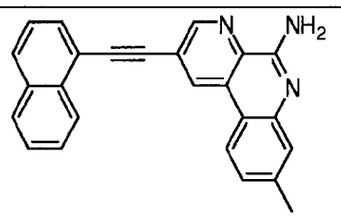
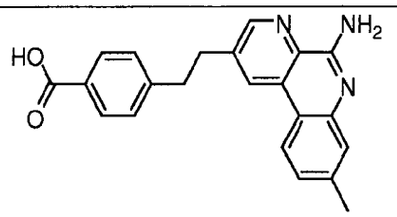
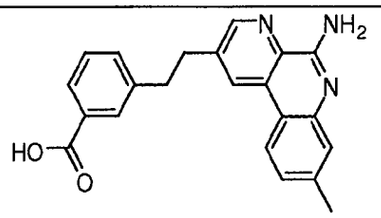
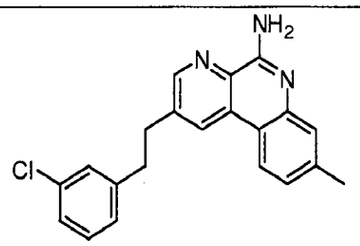
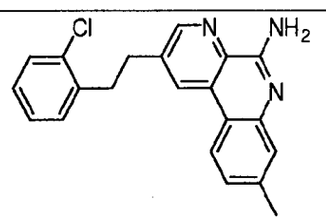
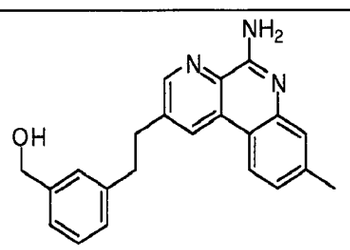
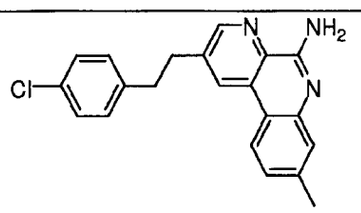
26		312.2
27		306.1
28		214.0
29		368.1
30		336.1
31		330.2
32		280.2
33		384.2
34		314.2

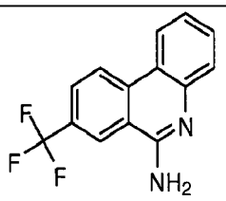
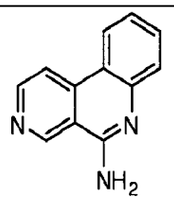
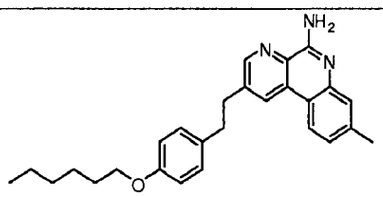
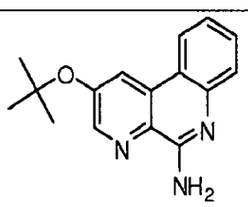
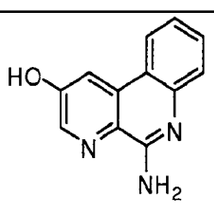
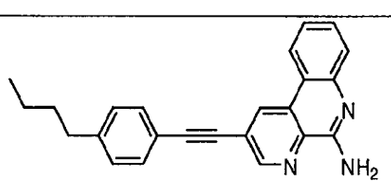
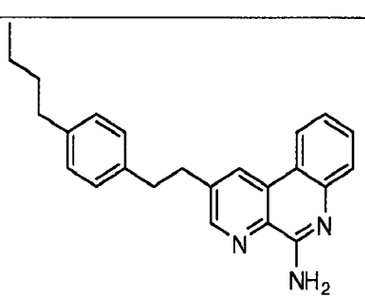
35		254.1
36		253.1
37		226.1
38		272.1
39		254.1
40		211.1
41		254.1
42		240.1

43		268.1
44		400.2
45		240.1
46		224.1
47		310.1
48		310.1
49		310.1
50		314.2

51		314.2
52		314.2
53		288.1
54		434.2
55		229.1
56		230.0
57		264.1
58		239.1

59		213.1
60		209.1
61		195.1
62		196.1
63		196.1
64		201.2
65		360.1
66		364.5
67		364.5

68		360.1
69		358.4
70		358.4
71		348.8
72		348.8
73		344.4
74		348.8

75		263.0
76		196.0
77		414.3
78		268.1
79		212.0
80		352.1
81		356.2
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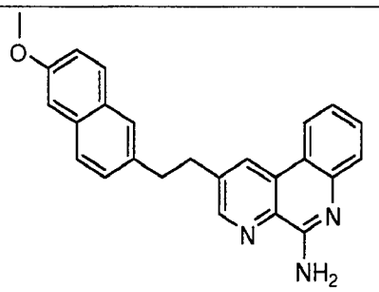
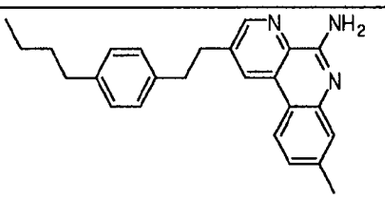
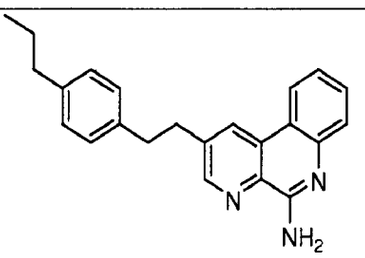
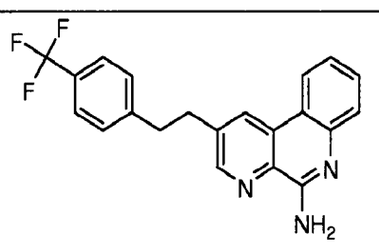
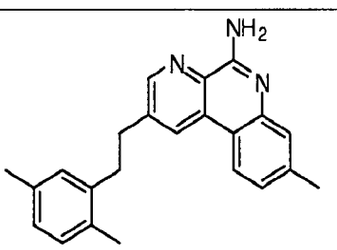
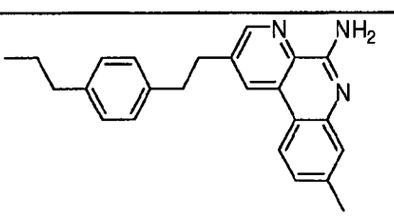
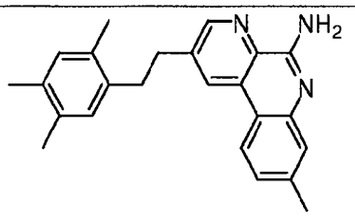
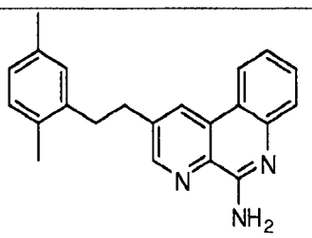
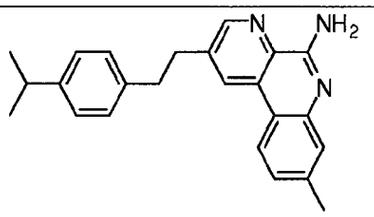
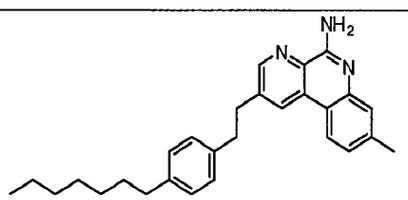
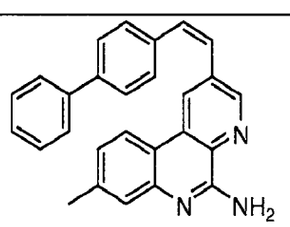
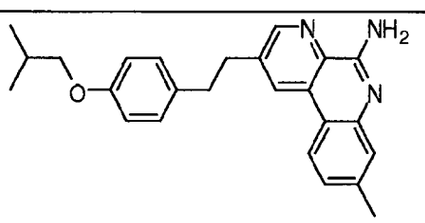
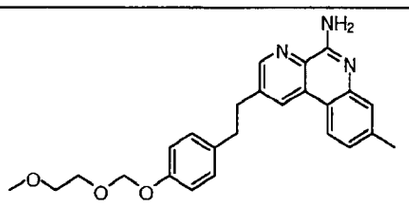
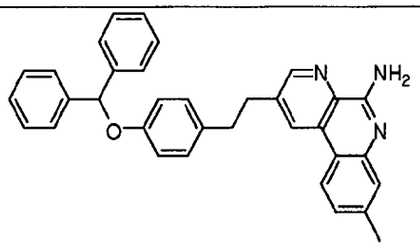
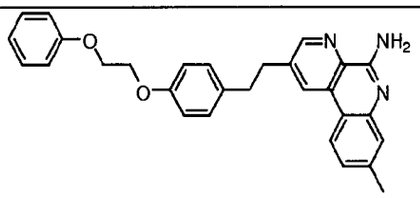
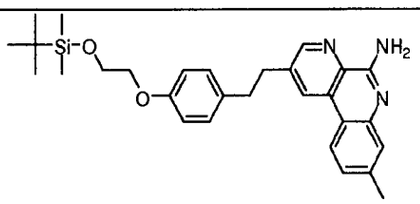
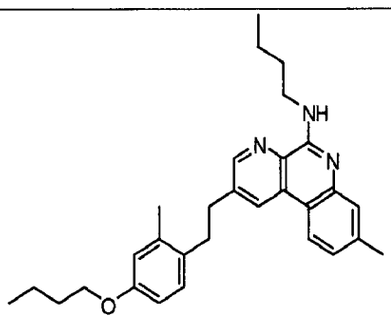
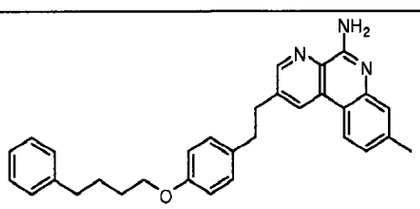
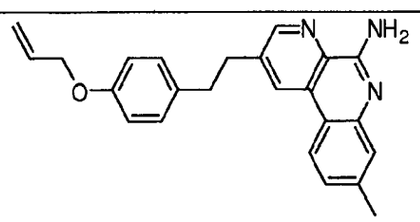
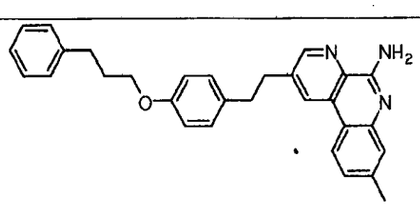
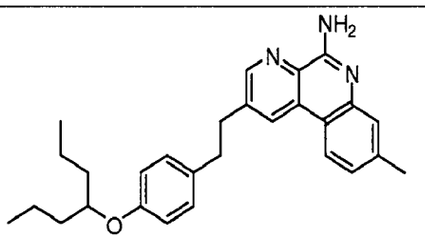
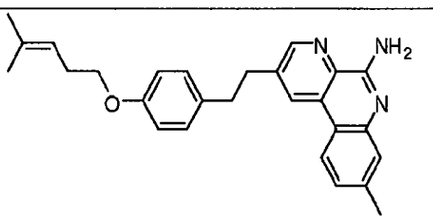
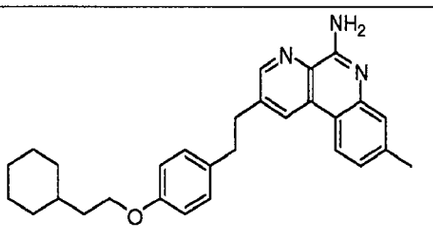
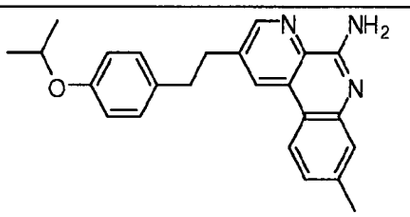
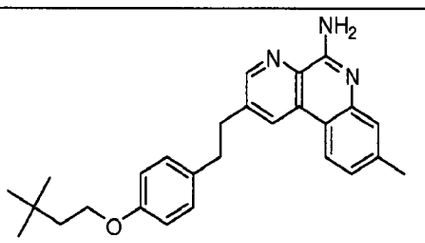
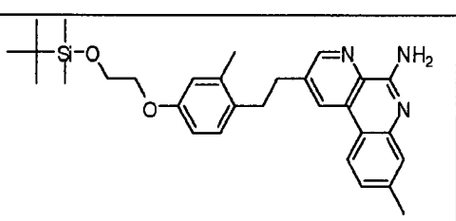
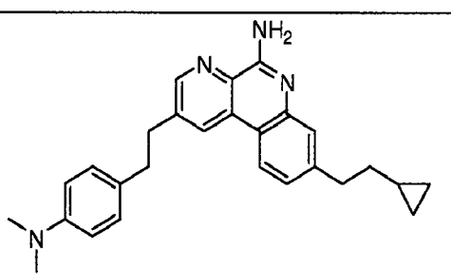
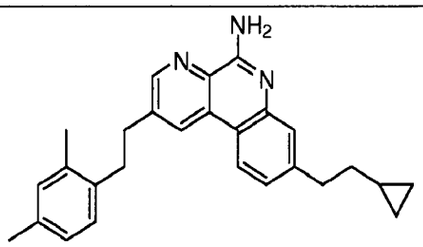
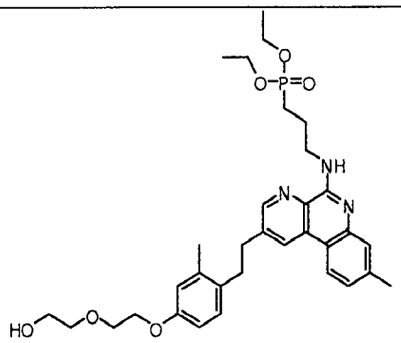
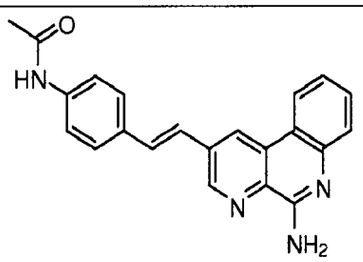
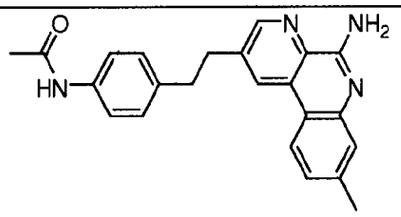
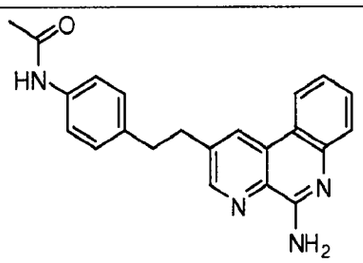
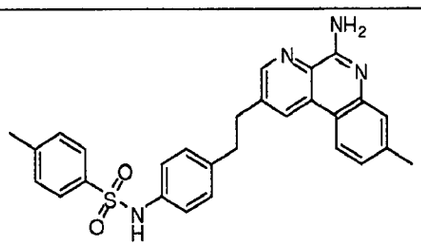
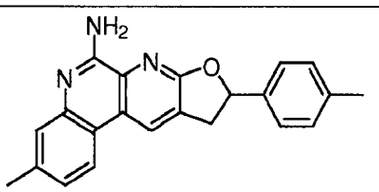
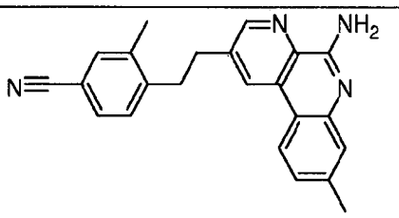
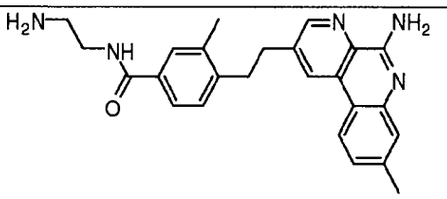
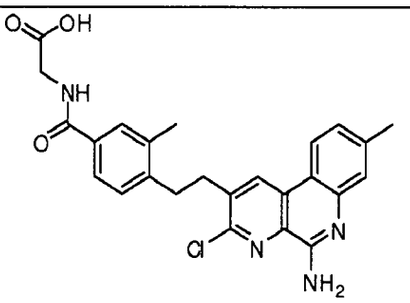
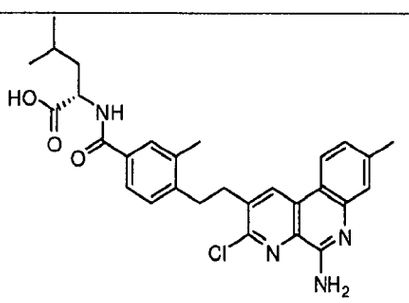
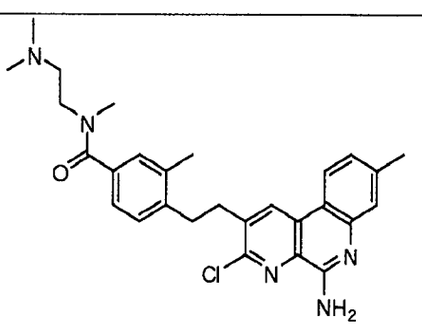
83		380.1
84		370.2
85		342.1
86		368.1
87		342.1
88		356.2

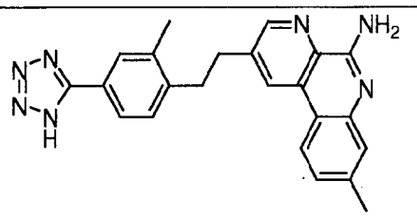
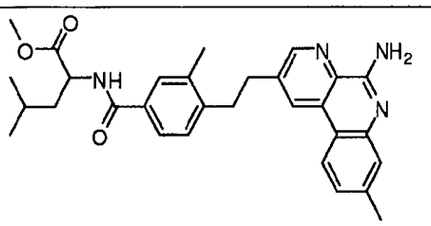
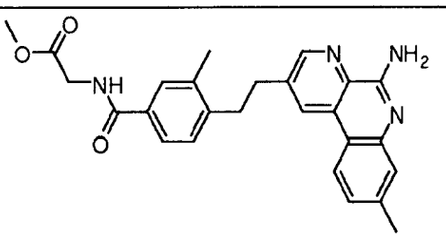
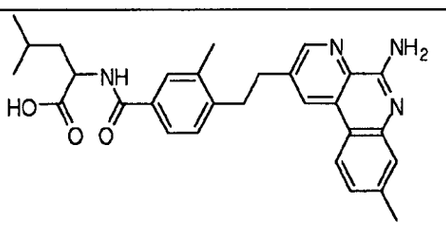
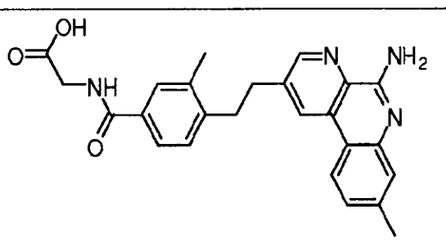
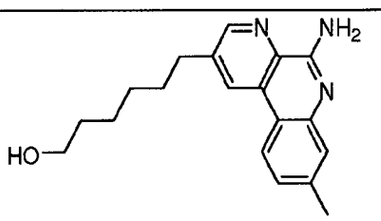
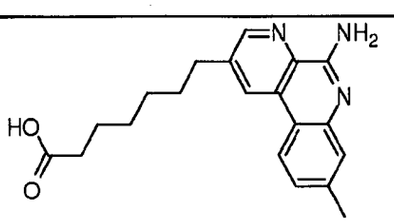
89		356.2
90		328.1
91		356.2
92		412.2
93		388.1
94		386.2
95		418.2

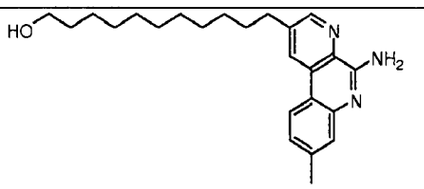
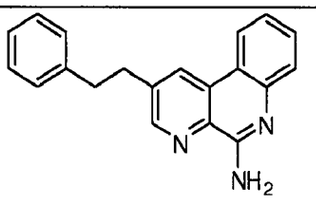
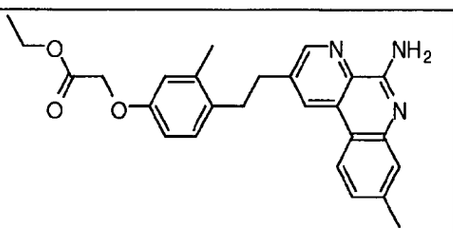
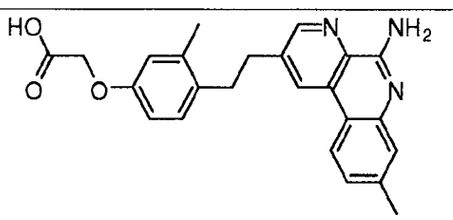
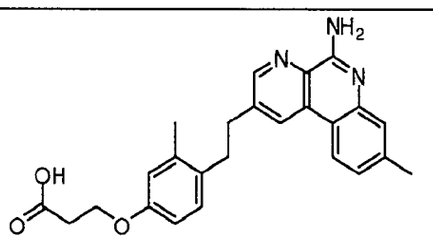
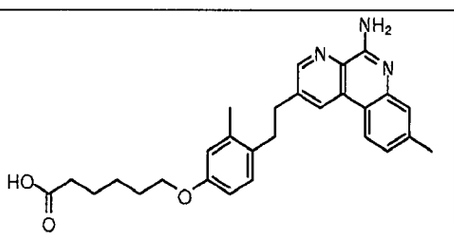
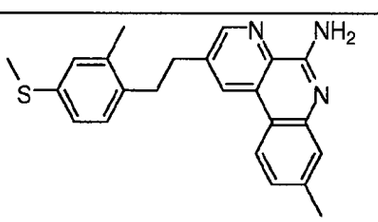
96		496.2
97		450.2
98		488.2
99		456.3
100		462.3
101		370.2
102		448.6

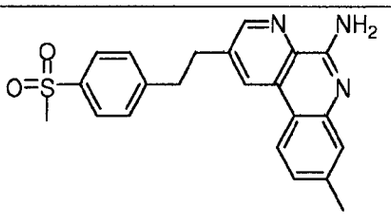
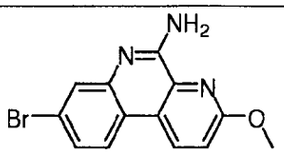
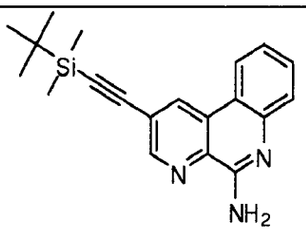
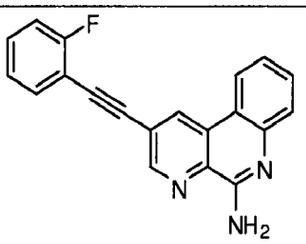
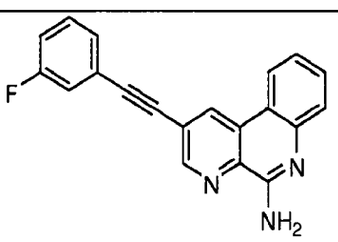
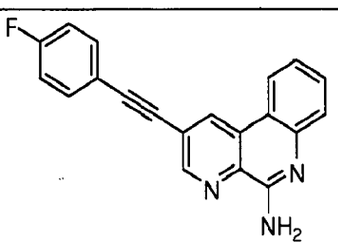
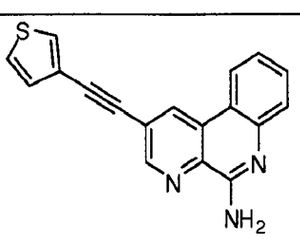
103		428.3
104		412.2
105		440.3
106		372.2
107		414.3
108		502.3
109		411.3

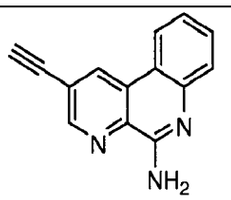
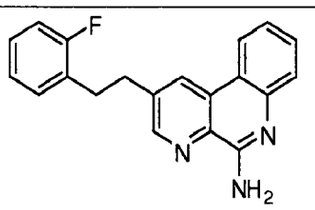
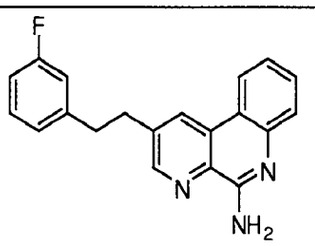
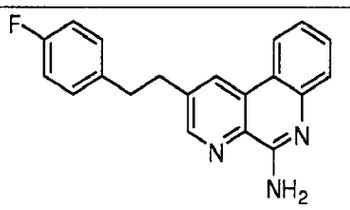
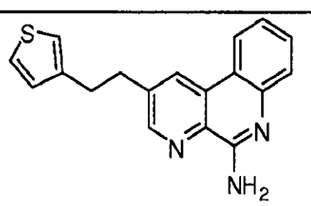
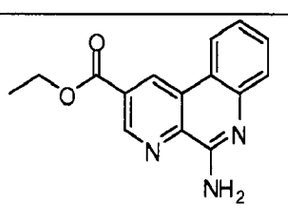
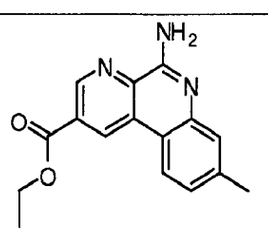
110		396.2
111		610.3
112		355.2
113		371.2
114		357.2
115		483.2

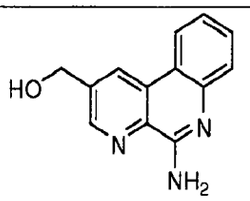
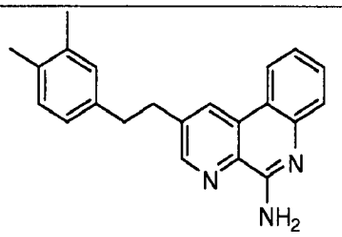
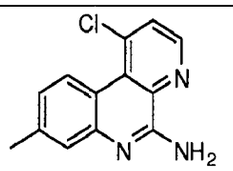
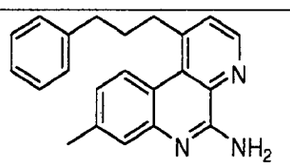
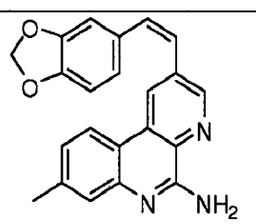
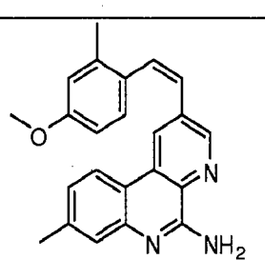
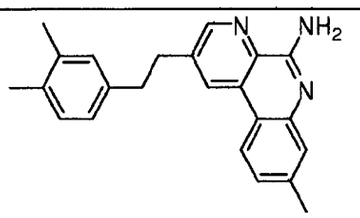
116		342.2
117		353.2
118		414.2
119		463.2
120		519.2
121		490.2

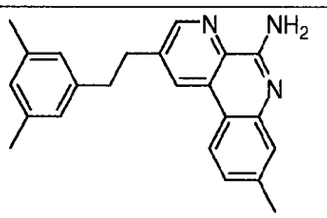
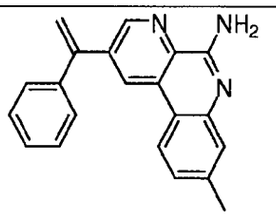
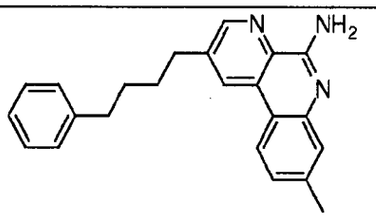
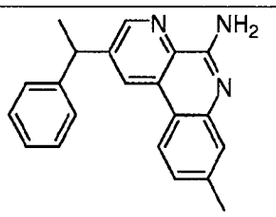
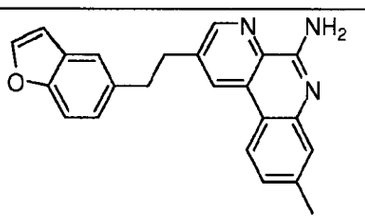
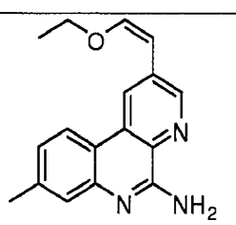
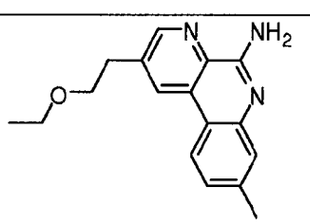
122		396.2
123		499.3
124		443.2
125		485.3
126		429.2
127		310.2
128		338.2

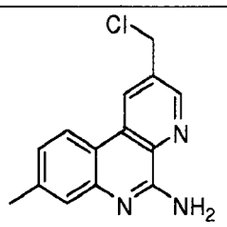
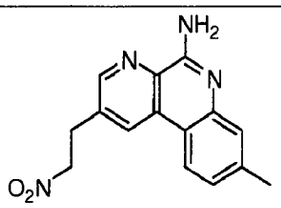
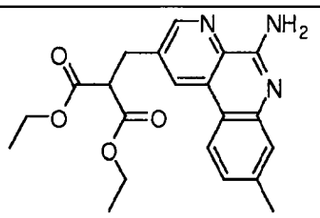
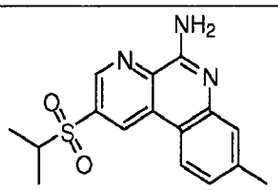
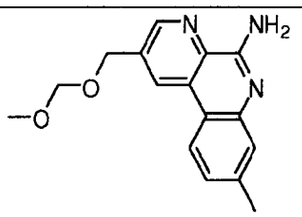
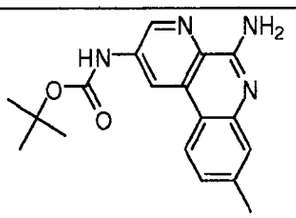
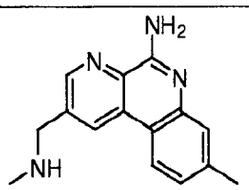
129		380.3
130		300.1
131		430.2
132		402.2
133		416.2
134		458.2
135		374.2

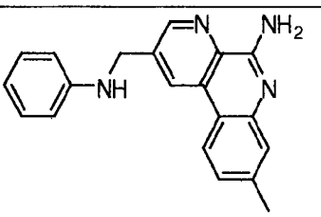
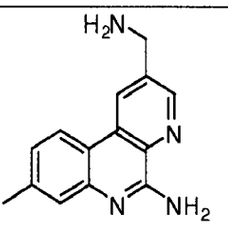
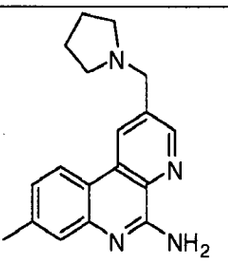
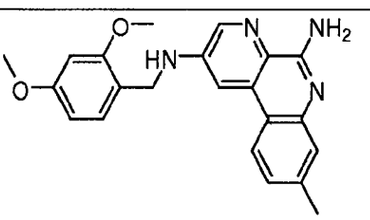
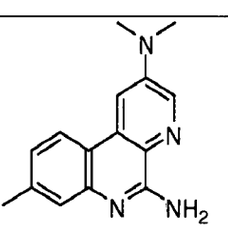
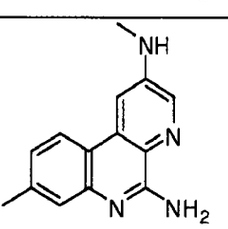
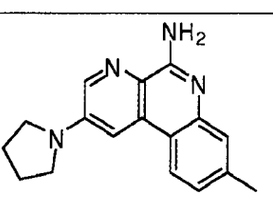
136		392.1
137		304.0
138		334.2
139		314.1
140		314.1
141		314.1
142		302.1

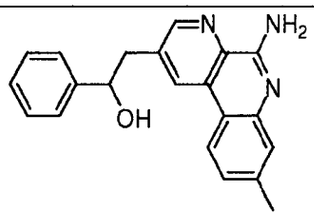
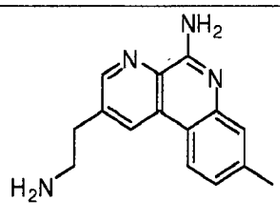
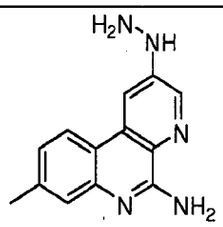
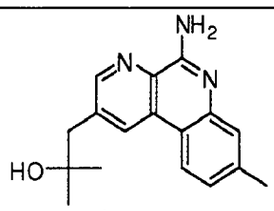
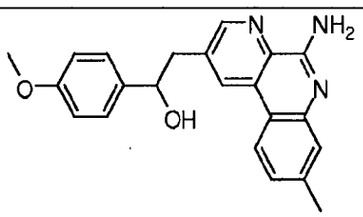
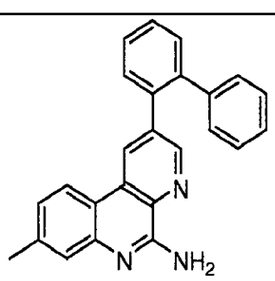
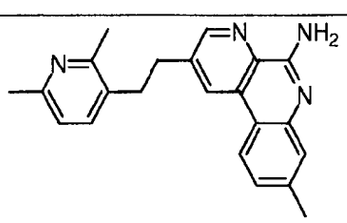
143		220.1
144		318.1
145		318.1
146		318.1
147		306.1
148		268.1
149		282.1

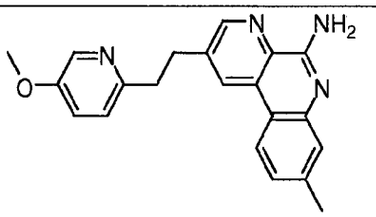
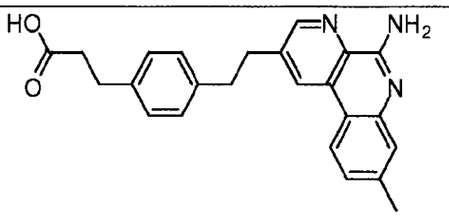
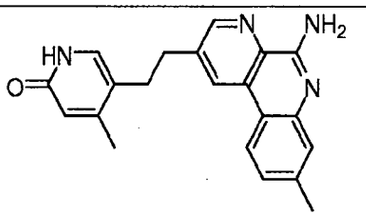
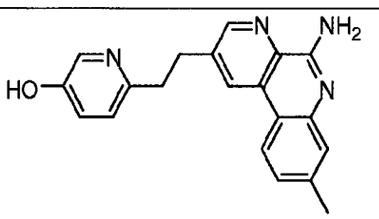
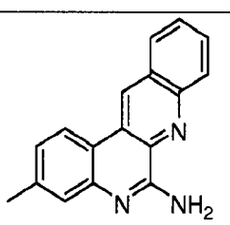
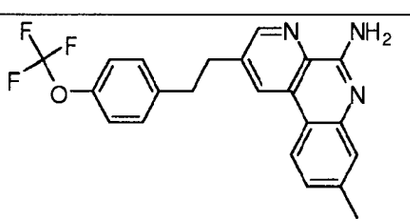
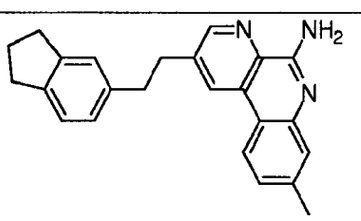
150		226.1
151		328.2
152		244.1
153		328.2
154		356.1
155		356.2
156		342.2

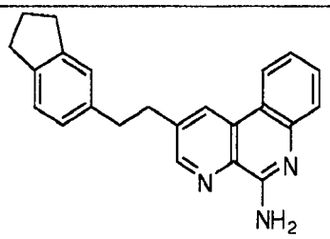
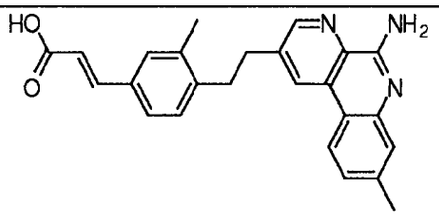
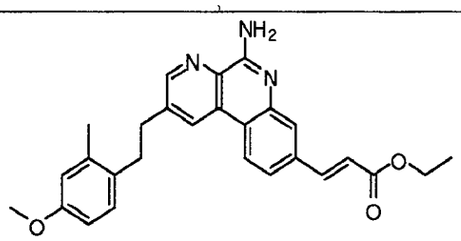
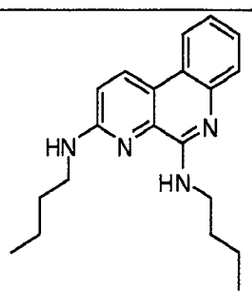
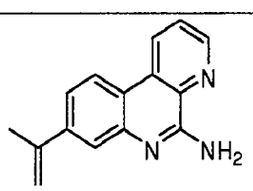
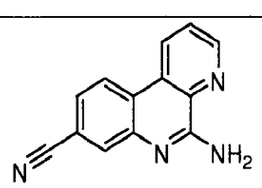
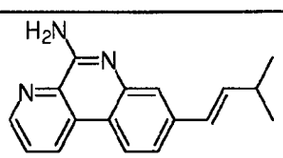
157		342.2
158		312.1
159		342.2
160		314.2
161		353.2
162		280.1
163		282.2

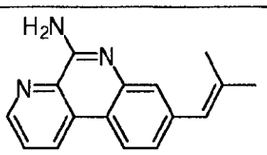
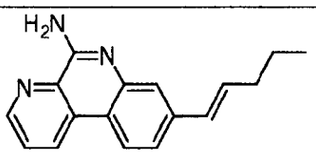
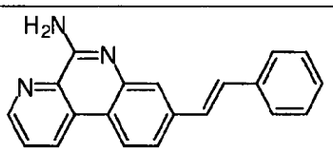
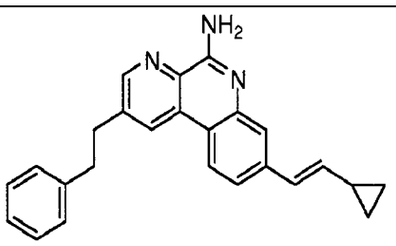
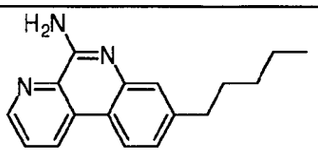
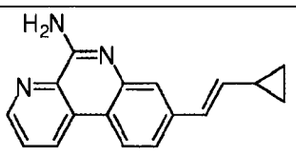
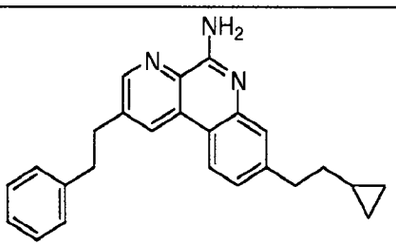
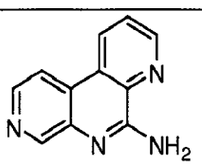
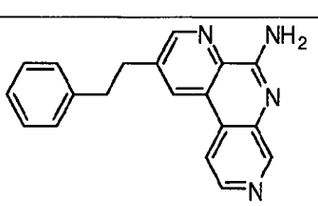
164		258.1
165		283.1
166		382.2 int
167		316.1
168		284.1
169		325.2
170		253.1

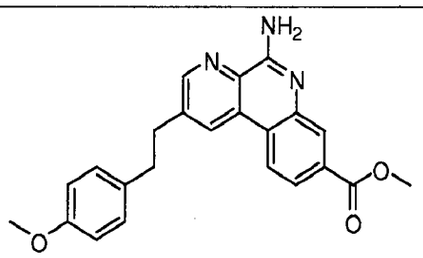
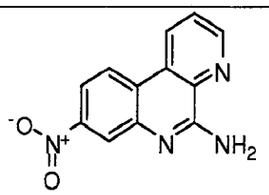
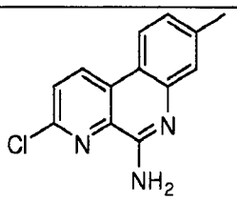
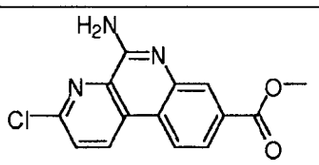
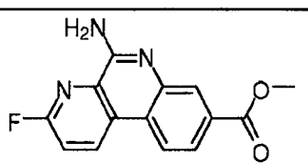
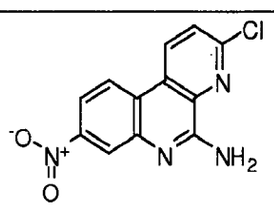
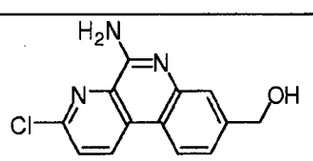
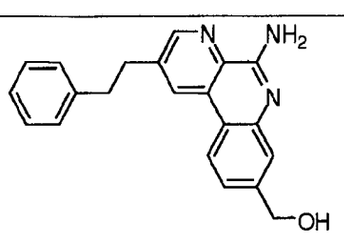
171		315.2
172		239.1
173		293.2
174		375.2
175		253.1
176		239.1
177		279.2

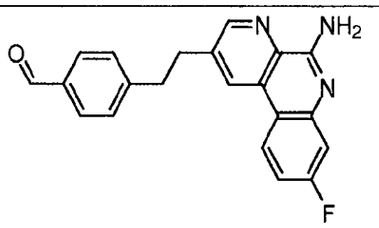
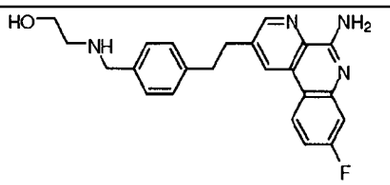
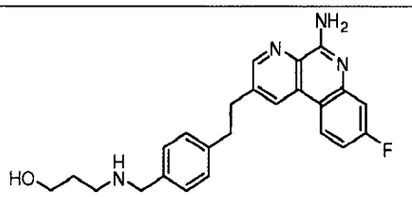
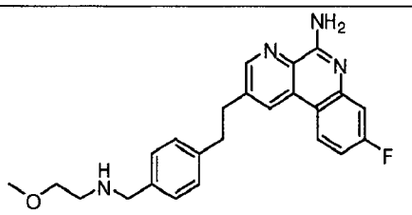
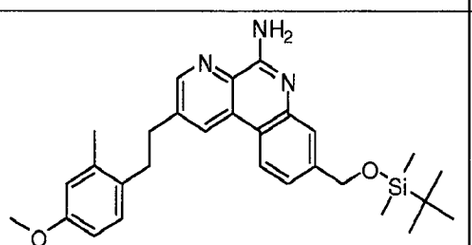
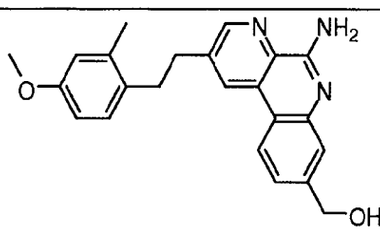
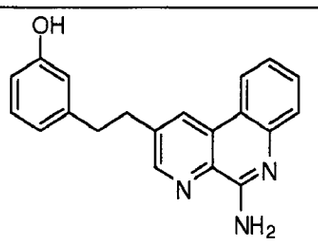
178		330.2
179		253.1
180		240.1
181		282.2
182		360.2
183		362.2
184		343.2

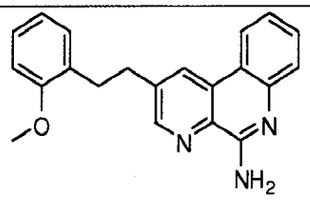
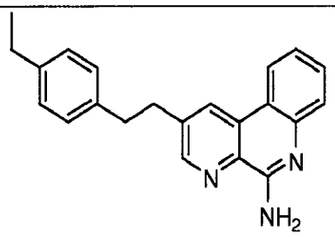
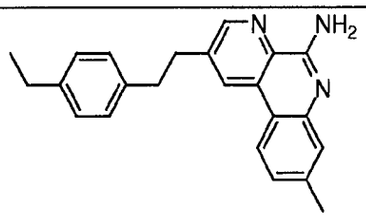
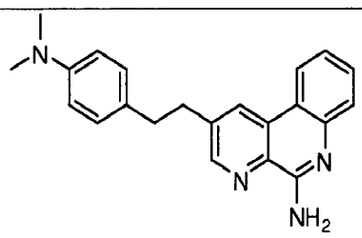
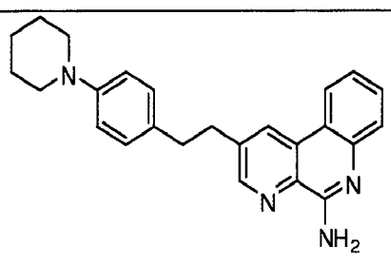
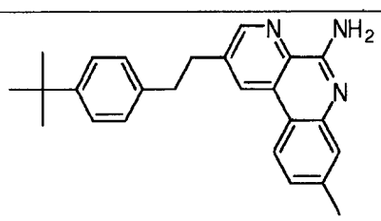
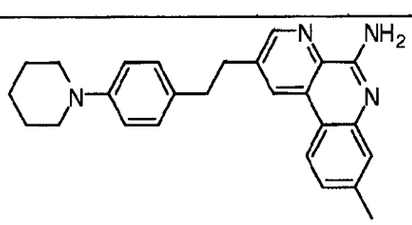
185		345.2
186		386.2
187		345.2
188		331.1
189		260.1
190		398.1
191		354.2

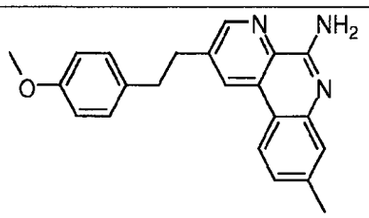
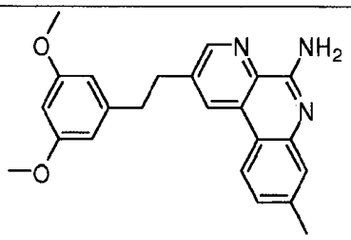
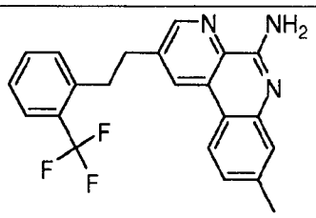
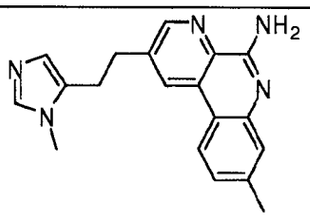
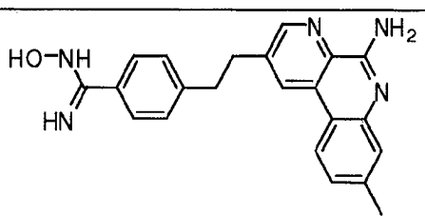
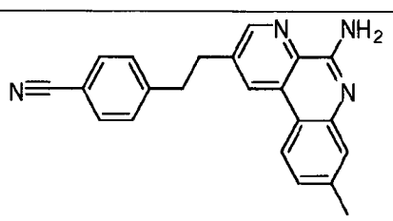
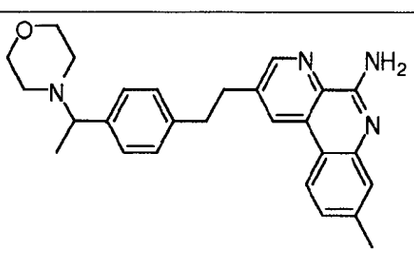
192		340.2
193		398.2
194		442.2
195		323.2
196		236.1
197		221.1
198		264.1

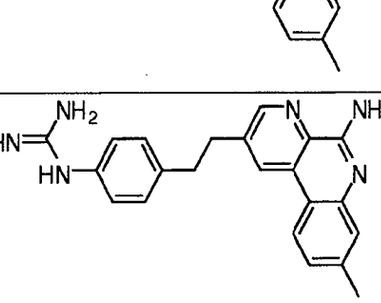
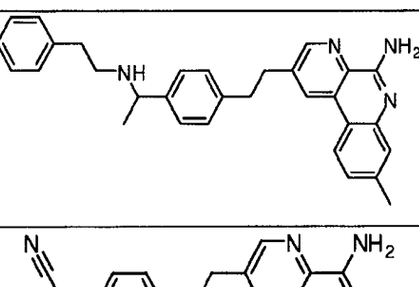
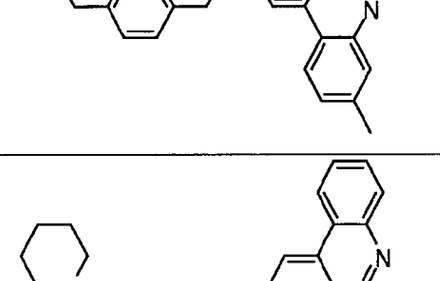
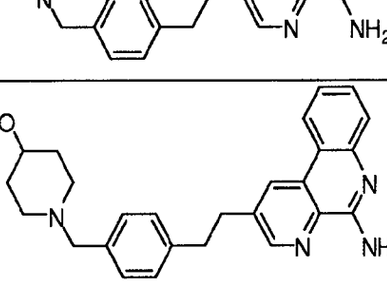
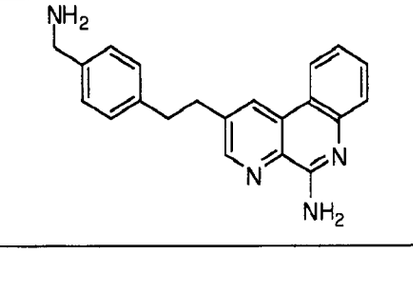
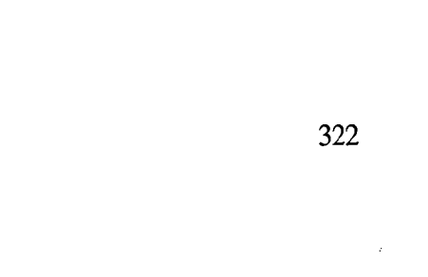
199		250.1
200		264.1
201		298.1
202		366.2
203		266.2
204		262.1
205		368.2
206		197.1
207		301.1

208		388.2
209		241.1
210		244.1
211		288.1
212		272.1
213		275.0
214		260.1
215		330.2

216		346.1
217		391.2
218		405.2
219		405.2
220		488.3
221		374.2
222		316.2

223		330.2
224		328.2
225		342.2
226		343.2
227		383.2
228		370.2
229		397.2

230		344.2
231		374.2
232		382.2
233		318.2
234		372.2
235		339.2
236		427.2

237		329.2
238		371.2
239		461.3
240		353.2
241		411.2
242		427.2
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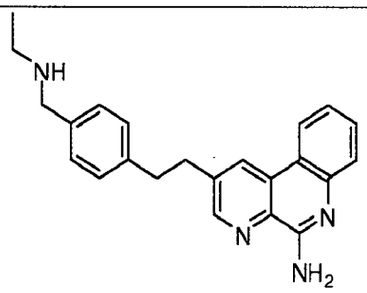
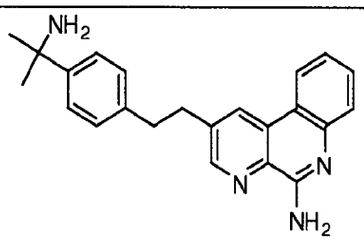
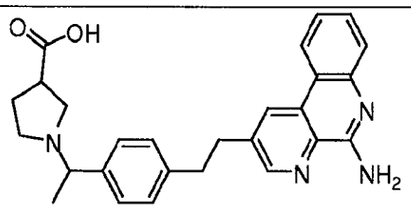
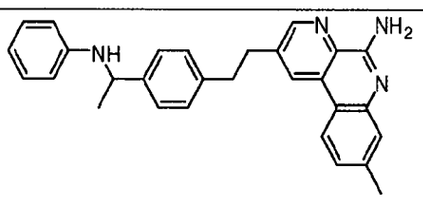
244		371.2
245		357.2
246		441.2
247		433.2

Example 198

In vivo Efficacy of Compounds at Enhancing an Immune Response

[000814] To demonstrate the ability of the compounds disclosed herein to enhance the immune response to a bacterial antigen when administered to a subject with the antigen, three compounds were used in conjunction with a recombinant *N. meningitidis* serogroup B vaccine. The vaccine, which is more fully described in Giuliani *et al.* (2006) *Proc Natl Acad Sci U S A* 103(29):10834-9 and WO2004/032958 – referred to herein as "3MenB," was tested *in vivo* in mice either with MF59 or with MF59 + one of the compounds disclosed herein. Mice were immunized with two doses administered intra muscularly with 3MenB/MF59 + one of six of the compounds or, as a positive control, an amount of a CpG oligonucleotide ("CpG"), R848, or Immiquimod (ImiQ). An additional positive control of 3MenB/MF59 + OMV (outer membrane vesicles derived from the *N. meningitidis* serogroup B strain NZ98/254) was also compared. The serum bactericidal antibody ("SBA") titer was assayed two weeks after the second dose using the standeard CFU method or Alamar Blue

method using a *N. meningitidis* serogroup strain NZ98. SBA titer is an FDA/EMEA accepted surrogate marker for efficacy of *N. meningitidis* vaccines in humans. The results are shown in Figure 1 (with the dose of the compound in μg indicated on the left). The fold-change over the response elicited with MF59/3MenB is shown to the right of each bar in Figure 1.

[000815] In a second experiment, the dose response of one compound, Example No. 47, was tested using the same protocol. Figure 2 shows the average result from three independent SBA studies with standard deviation shown as error bars. The SBA titers were measured in all cases using the standard CFU method. The dose of each compound in μg is indicated on the left of Figure 2.

[000816] Figure 3 shows the SBA titers from two independent studies comparing the dose response to Example No. 47 with 3MenB adjuvanted with alum in place of the MF59 adjuvant.

[000817] Figure 4 shows the SBA titers from another study comparing the dose response to another compound, Example No. 169.

[000818] Figure 5 summarizes the data from the six total experiments. A titer of > 1000 correlates with immunization providing protection against the pathogen tested in the SBA titer (i.e., the NZ/98 *N. meningitidis* serogroup B strain). Thus, at 100 μg, each of Example No. 47, Example No. 169, and Example No. 49 were able to provide a protective response in the mice thus demonstrating the ability of the compounds disclosed herein to enhance the immune response to an antigen. Only one of six experiments using 3MenB/MF59 produced a protective response against the NZ98 bacteria. By comparison, seven of eight experiments using the compounds disclosed herein produced a protective response against the NZ98 bacteria. ** and * above the compound in Figure 5 indicates a statistically significant difference by p-value between immunization with the compound and immunization without the compound (i.e., compared to the 3MenB/MF59 control). ns – indicates the difference was not statistically significant by p-value. Immunization with a CpG oligo versus Example No. 47 did not produce a statistically significant difference by p-value.

[000819] The body weight of the mice was measured at early (day 1 and day 2) and late (day 14 and day 28) time points after the immunization. Immunization with 3MenB/MF59 versus 3MenB/MF59 + Example No. 169 did not produce a statatistically significant different in weight drop. Mice immunized with a CpG oliogo or with the 3MenB/OMV did produce a slight, but statisticially significant weight drop on day one after immunization.

Assays

[000820] Compounds of Formula (I) provided herein are assayed to measure their capacity to modulate toll-like receptors.

Human peripheral blood mononuclear cell assay

[000821] The bioactivity of the described compounds are tested in the human peripheral blood assay (human PBMC) using a panel of independent normal human donors according to approved guidelines by the institutional review committee. Human PBMC are isolated from freshly peripheral blood using a Ficoll density gradient (GE healthcare 17-1440-03). 30-35mLs of peripheral human blood are layered onto 15mLs of Ficoll in 50 ml conical tubes, followed by centrifugation at 1800 rpm (Eppendorf Centrifuge 5810R with biohazard caps over the tube buckets) at room temperature for 30 minutes with no acceleration and no brake. The buffy layers are then collected and transferred onto new 50 ml conical tubes and washed twice in complete media consisting of RPMI 1640 (11875085 from Invitrogen Corporation, Carlsbad, California) supplemented with 10% heat inactivated fetal bovine serum (Gibco 10099-141), 1% Pen-Strep (Gibco#15140-122), 1 mM non essential amino acids (Gibco#11140-050), 1 mM sodium pyruvate (Gibco#11360-070), 2 mM L-Glutamine (Gibco#25030-081) and 1 mM HEPES (Gibco#15630-080). Viable cells are then counted using trypan blue staining, plated in 96 well flat bottom plates (Becton Dickinson #353070) at $2x10^5$ cells per well in 200 µl total volume of complete media. Compounds are then added in a 10 point dose response format starting at 100 µM, 3 fold dilution. Negative controls wells received equal concentration of DMSO. Culture supernatants are collected after 18-24 hours incubation at 37°C, 5% CO_2, stored at -20°C until further use.

[000822] IL-6 levels in the culture supernatants are measured using a Luminex kit (Biorad). Data analysis is performed using Prism software from GraphPad (San Diego, CA). Dose response curves are generated for each compound and EC50 values are determined as the concentration that gives 50% of the maximal signal.

Reporter gene assay

[000823] Human embryonic kidney 293 (HEK 293) cells are stably transfected with human TLR7 or TLR8 and an NF-kB-driven luciferase reporter vector (pNifty-Luciferase). As a control assay, normal Hek293 transfected with pNifty-Luc are used. Cells are cultured in DMEM supplemented with 2 mM L-glutamine, 10% heart inactivated FBS, 1% penicillin and streptomycin, 2 µg/ml puromycin (InvivoGen #ant-pr-5) and 5µg/ml of blasticidin (Invitrogen #46-1120). Bright-Glo™ Luciferase assay buffer and substrate are supplied by Promega #E263B and #E264B (assay substrate and buffer respectively). 384 well clear-bottom plates are supplied by Greiner bio-one (#789163-G) and are GNF custom bar-coded plates.

[000824] Cells are plated at 25,000 cells/well in 384-well plates in a final volume of 50 µl of

media. Cells are allowed to adhere to the plates after overnight (18 hours) culture at 37°C 5% CO_2. Serially diluted experimental and positive control compounds are then dispensed to each well and incubated for 7 hours at 37°C 5% CO_2. Cells stimulated with DMSO alone also serve as negative controls. After the incubation, 30 µl of the pre-mix assay buffer and substrate buffer are added to each well according to manufacturer's instructions. The luminescence signal is read on a CLIPR machine with an integration time of 20 seconds per plate.

[000825] Dose response curves are generated for each compound and EC50 values were determined as the concentration that gives 50% of the maximal signal.

Certain Assay Results

[000826] Various compounds of Formula (I)-(XVI) in free form or in pharmaceutically acceptable salt form, exhibit pharmacological properties, for example, as indicated by the *in vitro* tests described in this application. The EC_{50} value in those experiments is given as that concentration of the test compound in question that provoke a response halfway between the baseline and maximum responses. In certain examples compounds of Formula (I)-(XVI) have EC_{50} values from 1 nM to 200 µM. In some examples, compounds of Formula (I)-(XVI) have EC_{50} values from 0.01 µM to 100 µM. In other examples, compounds of Formula (I)-(XVI) have EC_{50} values from 0.01 µM to 50 µM. In other examples, compounds of Formula (I)-(XVI) have EC_{50} values from 0.01 µM to 25 µM. In other examples, compounds of Formula (I)-(XVI) have EC_{50} values from 0.01 µM to 20 µM. In other examples, compounds of Formula (I)-(XVI) have EC_{50} values from 0.01 µM to 15 µM. In other examples, compounds of Formula (I)-(XVI) have EC_{50} values from 0.01 µM to 10 µM. In other examples, compounds of Formula (I)-(XVI) have EC_{50} values from 0.01 µM to 5 µM. In other examples, compounds of Formula (I)-(XVI) have EC_{50} values from 0.01 µM to 2 µM. In other examples, compounds of Formula (I)-(XVI) have EC_{50} values from 0.01 µM to 1 µM. In certain examples such EC_{50} values are obtained relative to the activity of resiquimod set to 100%.

[000827] In other examples the following compounds of Formula (I)-(XVI) have EC_{50} values from 1 nM to 200 µM: 2-methylbenzo[f][1,7]naphthyridin-5-amine; 2-propylbenzo[f][1,7]naphthyridin-5-amine; 2-ethylbenzo[f][1,7]naphthyridin-5-amine; 2-(3-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; methyl 5-aminobenzo[f][1,7]naphthyridine-3-carboxylate; (5-aminobenzo[f][1,7]naphthyridin-3-yl)methanol; benzo[f][1,7]naphthyridin-5-amine; (5-aminobenzo[f][1,7]naphthyridin-8-

yl)methanol; 2-(2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-chlorobenzo[f][1,7]naphthyridin-5-amine; ethyl 5-aminobenzo[f][1,7]naphthyridine-9-carboxylate; 8-methoxybenzo[f][1,7]naphthyridin-5-amine; 8-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine; 8-fluorobenzo[f][1,7]naphthyridin-5-amine; 3-methylbenzo[f][1,7]naphthyridin-5-amine; 3-fluorobenzo[f][1,7]naphthyridin-5-amine; 2-phenethylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(naphthalen-1-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-(naphthalen-2-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoic acid; 3-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoic acid; 2-(3-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (3-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol; 2-(4-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-butylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-butylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-propylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,5-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-propylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2,4,5-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,5-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-isopropylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-heptylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-isobutoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-((2-methoxyethoxy)methoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-phenoxyethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-phenylbutoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(allyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(3-phenylpropoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(heptan-4-yloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-methylpent-3-enyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-cyclohexylethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-isopropoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(3,3-dimethylbutoxy)phenethyl)-8-

methylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide; N-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide; N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-4-methylbenzenesulfonamide; 3-methyl-9-p-tolyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzonitrile; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-aminoethyl)-3-methylbenzamide; 8-methyl-2-(2-methyl-4-(1H-tetrazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; methyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoate; methyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetic acid; 6-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)hexan-1-ol; 7-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)heptanoic acid; 11-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)undecan-1-ol; ethyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)acetate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)acetic acid; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propanoic acid; 6-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)hexanoic acid; 8-methyl-2-(2-methyl-4-(methylthio)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(methylsulfonyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(hexyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-phenethoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(pentyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(4-methylpentyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(thiophen-3-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; (5-aminobenzo[f][1,7]naphthyridin-2-yl)methanol; 2-(3,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3,4-dimethylphenethyl)-8-

methylbenzo[f][1,7]naphthyridin-5-amine; 2-(3,5-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(benzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-nitroethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(aminomethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; N^2,8-dimethylbenzo[f][1,7]naphthyridine-2,5-diamine; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-phenylethanol; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(4-methoxyphenyl)ethanol; 2-(biphenyl-2-yl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,6-dimethylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(5-methoxypyridin-2-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoic acid; 5-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-4-methylpyridin-2(1H)-one; 6-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)pyridin-3-ol; 8-methyl-2-(4-(trifluoromethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,3-dihydro-1H-inden-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(2,3-dihydro-1H-inden-5-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine; (E)-3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylic acid; (E)-ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylate; (E)-8-(2-cyclopropylvinyl)-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; 8-pentylbenzo[f][1,7]naphthyridin-5-amine; (E)-8-(2-cyclopropylvinyl)benzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-phenethylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-2-phenethylbenzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 3-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol; 2-(2-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-ethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-ethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(piperidin-1-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-tert-butylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(piperidin-1-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(3,5-dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(2-

(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-hydroxybenzimidamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzonitrile; 8-methyl-2-(4-(1-morpholinoethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-aminophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)guanidine; 8-methyl-2-(4-(1-(phenethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetonitrile; 2-(4-(piperidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzyl)piperidin-4-ol; 2-(4-(aminomethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-((ethylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-aminopropan-2-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 1-(1-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid; 8-methyl-2-(4-(1-(phenylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-ethyl-8-methylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)methanol; 8-methyl-2-propylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(1H-indol-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-ethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-phenoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2,4-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol; 2-(2-(2,3-dihydrobenzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethanol; 3-methyl-9-phenyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine; 8-methylbenzo[f][1,7]naphthyridine-2,5-diamine; 1-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)propan-2-ol; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetonitrile; N-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetamide; 2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(2,4-dimethylphenyl)ethanol; 2-(2-(6-methoxy-4-methylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)butan-1-ol; methyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-

yl)ethyl)phenyl)propanoate; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-1-ol; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-2-methylbutan-2-ol; 2-(4-(aminomethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; (E)-ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylate; ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoate; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzyl)propane-1,3-diol; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoic acid; 5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridine-8-carbaldehyde; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoate; 8-methyl-2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-2-ol; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol; ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoic acid; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)methanol; 8-methyl-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 8-methyl-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; (E)-3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylic acid; ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoate; 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoic acid; 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propan-1-ol; 5-aminobenzo[f][1,7]naphthyridin-8-ol; 5-aminobenzo[f][1,7]naphthyridine-8-carbaldehyde; 1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanol; 1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanone; 8-isopropylbenzo[f][1,7]naphthyridin-5-amine; 8-vinylbenzo[f][1,7]naphthyridin-5-amine; 8-ethylbenzo[f][1,7]naphthyridin-5-amine; 8-(methoxymethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; benzo[f][1,7]naphthyridine-5,8-diamine; 8-(aminomethyl)benzo[f][1,7]naphthyridin-5-amine; 3-fluoro-8-methylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-3-fluorobenzo[f][1,7]naphthyridin-8-yl)methanol; 3-chlorobenzo[f][1,7]naphthyridine-5,8-diamine; 3-fluorobenzo[f][1,7]naphthyridine-5,8-diamine; 8-isobutylbenzo[f][1,7]naphthyridin-5-amine; (E)-

8-(prop-1-enyl)benzo[f][1,7]naphthyridin-5-amine; 8-propylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)benzo[f][1,7]naphthyridin-5-amine; 8-phenethylbenzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(4-bromophenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 2-(4-methoxy-2-methylphenethyl)-8-pentylbenzo[f][1,7]naphthyridin-5-amine; 8-(2-cyclopropylethyl)-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; (5-amino-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; (2-(2-(1H-indol-5-yl)ethyl)-5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol; methyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,3-dimethylbenzamide; N-(2-acetamidoethyl)-4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide; 2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,N,3-trimethylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-hydroxyethyl)-3-methylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-3-methylbenzamide; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(pyrrolidin-1-yl)methanone; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(diethylamino)ethyl)-3-methylbenzamide; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(4-ethylpiperazin-1-yl)methanone; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(piperazin-1-yl)methanone; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methyl-N-(2-(pyrrolidin-1-yl)ethyl)benzamide; 4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N-methylbenzamide; 2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol; 2-(4-butoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(2-(biphenyl-4-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-((1,3-dihydroisobenzofuran-1-yl)methyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-methylallyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(isopentyloxy)phenethyl)-8-

methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl propyl carbonate; ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoate; 2-(4-(cyclopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(cyclobutylmethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 8-methyl-2-(4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-1-phenylethanone; 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)ethanol; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-N,N-dimethylacetamide; 8-methyl-2-(2-methyl-4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethanol; diethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonate; 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonic acid; 2-(4-butoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol; 2-(2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethanol; ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoate; 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoic acid; 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl ethyl carbonate; methyl 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoate; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoic acid; 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)butanoic acid; 2-(4-(isopentyloxy)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl hexyl carbonate; 2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine; (5-amino-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; diethyl 3-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)propylphosphonate; diethyl 3-(2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethoxy)propylphosphonate; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl dimethylsulfamate;

(5-amino-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol; 2-(4-(dimethylamino)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone; 2-(4-((dimethylamino)methyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(4-(1-(dimethylamino)ethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone oxime; 8-methyl-2-(4-((methylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; (4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzylamino)ethanol; 8-methyl-2-(4-(pyrrolidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 2-(3,4-dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)ethanol; 1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanol; 8-methyl-2-(4-(oxazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; 3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propanenitrile; (2R)-2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propan-1-ol; 8-methyl-2-(4-(1-(piperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; ((2S)-1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidin-2-yl)methanol; N^1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^2,N^2-dimethylethane-1,2-diamine; 3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propanoic acid; 8-methyl-2-(4-(1-(4-methylpiperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; N^2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^1,N^1-dimethylpropane-1,2-diamine; 8-methyl-2-(4-(1-(2-(pyridin-4-yl)ethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine; N^1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^2,N^2-diethylethane-1,2-diamine; 2-(4-(dimethylamino)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine; 1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid; 4-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)phenol; 1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2 yl)ethyl)phenyl)ethyl)pyrrolidin-3-ol; and 2-(4-(2-aminopropan-2-yl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine

[000828] By way of example only, the compound benzo[f][1,7]naphthyridin-5-amine (example

1) has an EC_{50} of >100μM , 14 μM and 0.84 μM in HEK293-TLR7, HEK293-TLR8 and IL-6 hPBMC assays, respectively.

[000829] By way of example only, the compound 8-methylbenzo[f][1,7]naphthyridin-5-amine (example 5) has an EC_{50} of 15.8 μM, 9.01 μM and 0.396 μM in HEK293-TLR7, HEK293-TLR8 and IL-6 hPBMC assays, respectively.

[000830] By way of example only, the compound 8-fluorobenzo[f][1,7]naphthyridin-5-amine (example 14) has an EC_{50} of 37 μM and 6.38 μM in HEK293-TLR8 and IL-6 hPBMC assays, respectively.

[000831] By way of example only, the compound 5-aminobenzo[f][1,7]naphthyridin-3(4H)-one (example 15) has an EC_{50} of 24.1 μM in a HEK293-TLR7 assay.

[000832] By way of example only, the compound 2-ethylbenzo[f][1,7]naphthyridin-5-amine (example 30) has an EC_{50} of 8.64 μM, 13 μM and 2.28 μM in HEK293-TLR7, HEK293-TLR8 and IL-6 hPBMC assays, respectively.

[000833] By way of example only, the compound 2-phenethylbenzo[f][1,7]naphthyridin-5-amine (example 33) has an EC_{50} of 2.44 μM and 2.28 μM in HEK293-TLR7 and IL-6 hPBMC assays.

[000834] By way of example only, the EC_{50} for TLR-7 stimulation by certain other compounds of Formula (I) are listed in Table 2 below. The identifying number for each compound is the number of the Example above that describes its synthesis

[000835]

Table 2

Example No.	Human TLR-7 EC_{50} (nM)
44	107
46	347
47	361
61	582
62	35
63	24
126	275
138	213
147	14
178	562

[000836] By way of example only, the EC_{50} for TLR-8 stimulation by certain other compounds of Formula (I) are listed in Table 3 below. The identifying number for each compound is the number of the Example above that describes its synthesis

Table 3

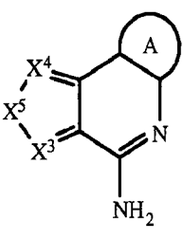
Example	Human TLR-8

No.	EC_{50} (μM)
177	15
186	11
187	82
188	>100
189	6.2
190	4.3
191	6
193	24
195	5.3
196	2.6

[000837] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

WE CLAIM:

1. A compound of Formula (I-A), or pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:



Formula (I-A)

wherein:

X^3 is N;

X^4 is N or CR^3;

X^5 is $-CR^4=CR^5-$;

R^1 and R^2 are H;

R^3 is H;

R^4 and R^5 are each independently selected from H, halogen, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-SR^7$, $-(CH_2)_nOR^7$, $-(CH_2)_nR^7$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, $-CN$, $-NO_2$, $-R^7$, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-C(O)N(R^9)_2$, $-S(O)_2R^8$, $-S(O)R^8$, $-S(O)_2N(R^9)_2$, and $-NR^9S(O)_2R^8$;

or R^3 and R^4, or R^4 and R^5, or R^5 and R^6, when present on adjacent ring atoms, can optionally be linked together to form a 5-6 membered ring, wherein the 5-6 membered ring is optionally substituted with R^7;

each L is independently selected from a bond, $-(O(CH_2)_m)_t-$, C_1-C_6alkyl, C_2-C_6alkenylene and C_2-C_6alkynylene, wherein the C_1-C_6alkyl, C_2-

C_6alkenylene and C_2-C_6alkynylene of L are each optionally substituted with 1 to 4 substituents independently selected from halogen, -R^8, -OR^8, -$N(R^9)_2$, -$P(O)(OR^8)_2$, -$OP(O)(OR^8)_2$, -$P(O)(OR^{10})_2$, and -$OP(O)(OR^{10})_2$;

R^7 is selected from H, C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6alkoxy, C_1-C_6haloalkoxy, and C_3-C_8heterocycloalkyl groups of R^7 are each optionally substituted with 1 to 3 R^{13} groups, and each R^{13} is independently selected from halogen, –CN, -LR^9, -LOR^9, -OLR^9, -LR^{10}, -LOR^{10}, -OLR^{10}, -LR^8, -LOR^8, -OLR^8, -LSR^8, -LSR^{10}, -$LC(O)R^8$, -$OLC(O)R^8$, -$LC(O)OR^8$, -$LC(O)R^{10}$, -$LOC(O)OR^8$, -$LC(O)NR^9R^{11}$, -$LC(O)NR^9R^8$, -$LN(R^9)_2$, -LNR^9R^8, -LNR^9R^{10}, -$LC(O)N(R^9)_2$, –$LS(O)_2R^8$, –$LS(O)R^8$, -$LC(O)NR^8OH$, -$LNR^9C(O)R^8$, -$LNR^9C(O)OR^8$, –$LS(O)_2N(R^9)_2$, -$OLS(O)_2N(R^9)_2$, -$LNR^9S(O)_2R^8$, -$LC(O)NR^9LN(R^9)_2$, -$LP(O)(OR^8)_2$, -$LOP(O)(OR^8)_2$, -$LP(O)(OR^{10})_2$ and -$OLP(O)(OR^{10})_2$;

each R^8 is independently selected from H, -$CH(R^{10})_2$, C_1-C_8alkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, C_1-C_6hydroxyalkyl and C_1-C_6haloalkoxy, wherein the C_1-C_8alkyl, C_2-C_8alkene, C_2-C_8alkyne, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, C_1-C_6hydroxyalkyl and C_1-C_6haloalkoxy groups of R^8 are each optionally substituted with 1 to 3 substituents independently selected from –CN, R^{11}, -OR^{11}, -SR^{11}, -$C(O)R^{11}$, -$OC(O)R^{11}$, -$C(O)N(R^9)_2$, -$C(O)OR^{11}$, -$NR^9C(O)R^{11}$, -NR^9R^{10}, -$NR^{11}R^{12}$, -$N(R^9)_2$, -OR^9, -OR^{10}, -$C(O)NR^{11}R^{12}$, -$C(O)NR^{11}OH$, –$S(O)_2R^{11}$, –$S(O)R^{11}$, –$S(O)_2NR^{11}R^{12}$, -$NR^{11}S(O)_2R^{11}$, -$P(O)(OR^{11})_2$, and -$OP(O)(OR^{11})_2$;

each R^9 is independently selected from H, -$C(O)R^8$, -$C(O)OR^8$, -$C(O)R^{10}$, -$C(O)OR^{10}$, -$S(O)_2R^{10}$, -C_1-C_6 alkyl, C_1-C_6 heteroalkyl and C_3-C_6 cycloalkyl, or each R^9 is independently a C_1-C_6alkyl that together with N they are attached to form a C_3-C_8heterocycloalkyl, wherein the C_3-

C_8heterocycloalkyl ring optionally contains an additional heteroatom selected from N, O and S, and wherein the C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, or C_3-C_8heterocycloalkyl groups of R^9 are each optionally substituted with 1 to 3 substituents independently selected from –CN, R^{11}, -OR^{11}, -SR^{11}, -$C(O)R^{11}$, -$OC(O)R^{11}$, -$C(O)OR^{11}$, -$NR^{11}R^{12}$, -$C(O)NR^{11}R^{12}$, -$C(O)NR^{11}OH$, -$S(O)_2R^{11}$, -$S(O)R^{11}$, -$S(O)_2NR^{11}R^{12}$, -$NR^{11}S(O)_2R^{11}$, -$P(O)(OR^{11})_2$, and -$OP(O)(OR^{11})_2$;

each R^{10} is independently selected from aryl, C_3-C_8cycloalkyl, C_3-C_8heterocycloalkyl and heteroaryl, wherein the aryl, C_3-C_8cycloalkyl, C_3-C_8heterocycloalkyl and heteroaryl groups are optionally substituted with 1 to 3 substituents selected from halogen, $-R^8$, -OR^8, $-LR^9$, -LOR^9, -$N(R^9)_2$, -$NR^9C(O)R^8$, -$NR^9CO_2R^8$, -CO_2R^8, -$C(O)R^8$ and -$C(O)N(R^9)_2$;

R^{11} and R^{12} are independently selected from H, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl groups of R^{11} and R^{12} are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, R^8, $-OR^8$, -$C(O)R^8$, -$OC(O)R^8$, -$C(O)OR^8$, -$N(R^9)_2$, -$NR^8C(O)R^8$, -$NR^8C(O)OR^8$, -$C(O)N(R^9)_2$, C_3-C_8heterocycloalkyl, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, -$NR^9S(O)_2R^8$, C_1-C_6haloalkyl and C_1-C_6haloalkoxy;

or R^{11} and R^{12} are each independently C_1-C_6alkyl and taken together with the N atom to which they are attached form an optionally substituted C_3-C_8heterocycloalkyl ring optionally containing an additional heteroatom selected from N, O and S;

Ring A is an aryl or a heteroaryl, wherein the aryl and heteroaryl groups of Ring A are optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, -OR^7, -OR^8, $-R^{10}$, -OR^{10}, -SR^8, -NO_2, -CN, -$N(R^9)_2$, -$NR^9C(O)R^8$, -$NR^9C(S)R^8$, -$NR^9C(O)N(R^9)_2$, -$NR^9C(S)N(R^9)_2$, -$NR^9CO_2R^8$, -$NR^9NR^9C(O)R^8$, -$NR^9NR^9C(O)N(R^9)_2$, -$NR^9NR^9CO_2R^8$, -$C(O)C(O)R^8$, -$C(O)CH_2C(O)R^8$, -CO_2R^8, -$(CH_2)_nCO_2R^8$, -$C(O)R^8$, -$C(S)R^8$, -$C(O)N(R^9)_2$, -$C(S)N(R^9)_2$, -$OC(O)N(R^9)_2$, -$OC(O)R^8$,

-C(O)N(OR^8)R^8, -C(NOR^8)R^8, -S(O)$_2$R^8, -S(O)$_3$R^8, -SO$_2$N(R^9)$_2$, -S(O)R^8, -NR^{9}SO$_2$N(R^9)$_2$, -NR^{9}SO$_2$R^8, -P(O)(OR^8)$_2$, -OP(O)(OR^8)$_2$, -P(O)(OR^{10})$_2$, -OP(O)(OR^{10})$_2$, -N(OR^8)R^8, -CH=CHCO$_2$R^8, -C(=NH)-N(R^9)$_2$, and -(CH$_2$)$_n$NHC(O)R^8; or two adjacent R^A substituents on Ring A form a 5-6 membered ring that contains up to two heteroatoms as ring members;

n is, independently at each occurrence, 0, 1, 2, 3, 4, 5, 6, 7 or 8;

each m is independently selected from 1, 2, 3, 4, 5 and 6, and

t is 1, 2, 3, 4, 5, 6, 7 or 8.

2. The compound of claim 1, wherein:

one of R^4 and R^5 is H;

and the other of R^4 and R^5 is selected from halogen, -C(O)OR^7, -C(O)R^7, -C(O)N(R^{11}R^{12}), -N(R^{11}R^{12}), -N(R^9)$_2$, -NHN(R^9)$_2$, -LR^8, -LR^{10}, -OLR^8, -OLR^{10}, -SR^7, -(CH$_2$)$_n$OR^7, -(CH$_2$)$_n$R^7, C$_1$-C$_6$alkyl, C$_1$-C$_6$heteroalkyl, C$_1$-C$_6$haloalkyl, C$_2$-C$_8$alkene, C$_2$-C$_8$alkyne, C$_1$-C$_6$alkoxy, C$_1$-C$_6$haloalkoxy, aryl, heteroaryl, C$_3$-C$_8$cycloalkyl, and C$_3$-C$_8$heterocycloalkyl, wherein the C$_1$-C$_6$alkyl, C$_1$-C$_6$heteroalkyl, C$_1$-C$_6$haloalkyl, C$_2$-C$_8$alkene, C$_2$-C$_8$alkyne, C$_1$-C$_6$alkoxy, C$_1$-C$_6$haloalkoxy, aryl, heteroaryl, C$_3$-C$_8$cycloalkyl, and C$_3$-C$_8$heterocycloalkyl groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, -R^7, -OR^8, -C(O)R^8, -OC(O)R^8, -C(O)OR^8, -N(R^9)$_2$, -P(O)(OR^8)$_2$, -OP(O)(OR^8)$_2$, -P(O)(OR^{10})$_2$, -OP(O)(OR^{10})$_2$, -C(O)N(R^9)$_2$, –S(O)$_2$R^8, –S(O)$_2$N(R^9)$_2$, and -NR^{9}S(O)$_2$R^8.

3. The compound of any of claims 1-2, wherein Ring A is phenyl, naphthyl, fluorenyl, indenyl, azulenyl or anthracenyl, each of which is optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from –R^8, –R^7, -OR^7, -OR^8, –R^{10}, -OR^{10}, -SR^8, -NO$_2$, -CN, -N(R^9)$_2$, -NR^{9}C(O)R^8, -NR^{9}C(S)R^8, -NR^{9}C(O)N(R^9)$_2$, -NR^{9}C(S)N(R^9)$_2$, -NR^{9}CO$_2$R^8, -NR^{9}NR^{9}C(O)R^8, -NR^{9}NR^{9}C(O)N(R^9)$_2$, -NR^{9}NR^{9}CO$_2$R^8, -C(O)C(O)R^8, -C(O)CH$_2$C(O)R^8, -CO$_2$R^8, -(CH$_2$)$_n$CO$_2$R^8, -C(O)R^8, -C(S)R^8, -C(O)N(R^9)$_2$, -C(S)N(R^9)$_2$, -OC(O)N(R^9)$_2$, -OC(O)R^8, -C(O)N(OR^8)R^8, -C(NOR^8)R^8, -S(O)$_2$R^8, -S(O)$_3$R^8, -SO$_2$N(R^9)$_2$, -S(O)R^8, -NR^{9}SO$_2$N(R^9)$_2$, -NR^{9}SO$_2$R^8, -P(O)(OR^8)$_2$, -OP(O)(OR^8)$_2$, -P(O)(OR^{10})$_2$, -

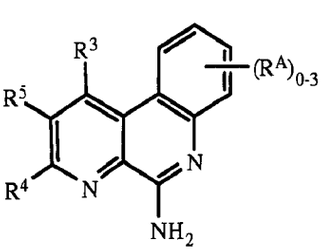
$OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$.

4. The compound of claim 3, wherein Ring A is phenyl or naphthyl.

5. The compound of any of claims 1-2, wherein Ring A is benzofuranyl, benzofurazanyl, benzoxazolyl, benzopyranyl, benzthiazolyl, benzothienyl, benzazepinyl, benzimidazolyl, benzothiopyranyl, benzo[1,3]dioxole, benzo[b]furyl, benzo[b]thienyl, cinnolinyl, furazanyl, furyl, furopyridinyl, imidazolyl, indolyl, indolizinyl, indolin-2-one, indazolyl, isoindolyl, isoquinolinyl, isoxazolyl, isothiazolyl, 1,8-naphthyridinyl, oxazolyl, oxaindolyl, oxadiazolyl, pyrazolyl, pyrrolyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinoxalinyl, quinolinyl, quinazolinyl, 4H-quinolizinyl, thiazolyl, thiadiazolyl, thienyl, triazinyl,triazolyl or tetrazolyl, each of which is optionally substituted with 1 to 3 R^A groups, wherein each R^A is independently selected from $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, -CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, and $-(CH_2)_nNHC(O)R^8$.

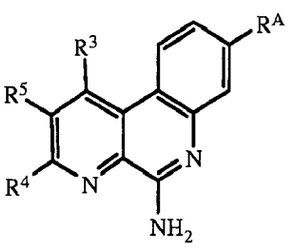
6. The compound of claim 5, wherein Ring A is pyridyl, benzo[1,3]dioxole, thienyl, benzothienyl, benzofuranyl, or indolyl.

7. The compound of any of claims 1-3, wherein the compound has a structure of Formula (X-A):



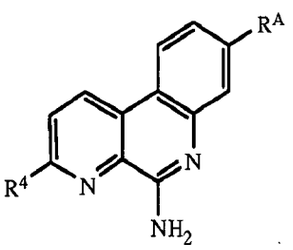
Formula (X-A).

8. The compound of claim 7, wherein the compound has a structure of Formula (XI):

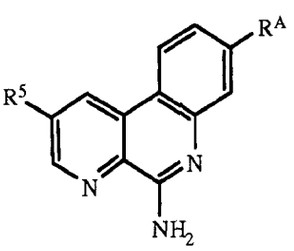


Formula (XI).

9. The compound of any of claims 1-8, wherein the compound has a structure of Formula (XII) or Formula (XIII):



Formula (XII)



Formula (XIII).

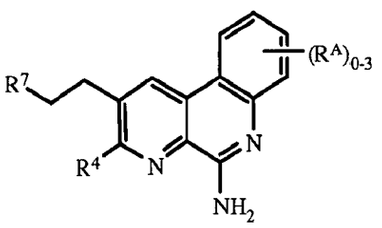
10. The compound of any of claims 1-9, wherein,

R^4 and R^5 are independently selected from H, halogen, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, $-SR^7$, $-(CH_2)_nR^7$, $-(CH_2)_nOR^7$, $-C_1$-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy, wherein the C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy groups of R^4 and R^5 are each optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, $-R^7$, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-C(O)N(R^9)_2$, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, and $-NHS(O)_2R^8$.

11. The compound of any of claims 1-10, wherein,

R^4 and R^5 are independently selected from H, halogen, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, $-SR^7$, $-(CH_2)_nOR^7$, $-(CH_2)_nR^7$, $-C_1$-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy, wherein the $-C_1$-C_6alkyl, C_1-C_6haloalkyl, C_2-C_8alkene, C_2-C_8alkyne and C_1-C_6alkoxy groups are each optionally substituted with R^7.

12. The compound of any of claims 1-11, wherein the compound has a structure of Formula (XIV):



Formula (XIV).

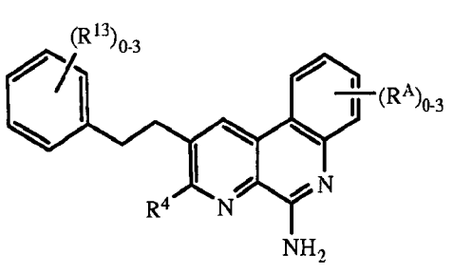
13. The compound of any of claims 1-12, wherein,

R^7 is selected from H, C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl and C_3-C_8heterocycloalkyl groups of R^7 are each optionally substituted with 1 to 3 R^{13} groups and each R^{13} is independently selected from halogen, –CN, -LR^9, -LOR^9, -OLR^9, -LR^{10}, -LOR^{10}, -OLR^{10}, -LR^8, -LOR^8, -OLR^8, -LSR^8, -LSR^{10}, -LC(O)R^8, -OLC(O)R^8, -LC(O)OR^8, -LC(O)R^{10}, -LOC(O)OR^8, -LC(O)NR^9R^{11}, -LC(O)NR^9R^8, -LN$(R^9)_2$, -LNR^9R^8, -LNR^9R^{10}, -LC(O)N$(R^9)_2$, –LS$(O)_2R^8$, –LS(O)R^8, -LC(O)NR^8OH, -LNR^9C(O)R^8, -LNR^9C(O)OR^8, –LS$(O)_2$N$(R^9)_2$, -OLS$(O)_2$N$(R^9)_2$, -LNR^9S$(O)_2R^8$, -LC(O)NR^9LN$(R^9)_2$, -LP(O)$(OR^8)_2$, -LOP(O)$(OR^8)_2$, -LP(O)$(OR^{10})_2$ and -OLP(O)$(OR^{10})_2$.

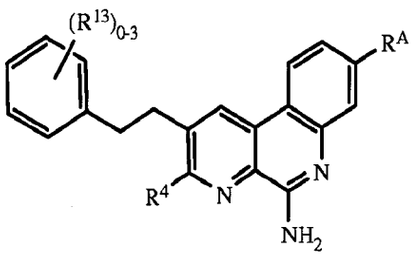
14. The compound of any of claims 1-13, wherein,

R^7 is selected from H, C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl, wherein the C_1-C_6alkyl, aryl, heteroaryl, C_3-C_8cycloalkyl, and C_3-C_8heterocycloalkyl groups are each optionally substituted with 1-3 R^{13} groups and each R^{13} is independently selected from halogen, C_1-C_6haloalkyl, -LR^8, LR^9, -LOR^8 and -OLR^8.

15. The compound of any of claims 1-14, wherein the compound has a structure of Formula (XV) or Formula (XVI):



Formula (XV),



Formula (XVI).

16. The compound of any of claims 1-15, wherein,

R^{13} is selected from -LR^9, -LOR^9, -OLR^9, -LR^{10}, -LOR^{10}, -OLR^{10}, -LR^8, -LOR^8, -OLR^8, -LSR^8, -LSR^{10}, -LC(O)R^8, -OLC(O)R^8, -LC(O)OR^8, -LC(O)R^{10}, -LOC(O)OR^8, -LC(O)NR^9R^{11}, -LC(O)NR^9R^8, -LN$(R^9)_2$, -LNR^9R^8, -LNR^9R^{10}, -LC(O)N$(R^9)_2$, –LS(O)$_2R^8$,–LS(O)R^8, -LC(O)NR^8OH, -LNR^9C(O)R^8, -LNR^9C(O)OR^8, –LS(O)$_2$N$(R^9)_2$, -OLS(O)$_2$N$(R^9)_2$, -LNR^9S(O)$_2R^8$, -LC(O)NR^9LN$(R^9)_2$, -LP(O)$(OR^8)_2$, -LOP(O)$(OR^8)_2$, -LP(O)$(OR^{10})_2$ and -OLP(O)$(OR^{10})_2$.

17. The compound of any of claims 1-16, wherein,

R^{10} is an aryl or a heteroaryl, wherein the aryl and heteroaryl groups are optionally substituted with 1 to 3 substituents selected from halogen, –R^8, -OR^8, –LR^9, -LOR^9 and -N$(R^9)_2$.

18. The compound of any of claims 1-17, wherein,

R^{10} is phenyl optionally substituted with 1 to 3 substituents selected from halogen, –R^8, -OR^8, and -N$(R^9)_2$.

19. The compound of any of claims 1-18, wherein,

each R^A is independently selected from –R^7, -OR^7, –R^8, -OR^8, –R^{10}, -OR^{10}, -SR^8, -N$(R^9)_2$, -S(O)$_2R^8$, -S(O)$_3R^8$, -SO$_2$N$(R^9)_2$, -S(O)R^8, -NR^9SO$_2$N$(R^9)_2$, -CH=CHCO$_2R^8$, $(CH_2)_n$CO$_2R^8$, -NR^9SO$_2R^8$, -P(O)$(OR^8)_2$, -OP(O)$(OR^8)_2$, -P(O)$(OR^{10})_2$, and -OP(O)$(OR^{10})_2$.

20. The compound of any of claims 1-19, wherein,

R^8 is selected from H, C_1-C_6alkyl and C_1-C_6haloalkyl.

21. The compound of claim 1 selected from

2-methylbenzo[f][1,7]naphthyridin-5-amine,

2-propylbenzo[f][1,7]naphthyridin-5-amine,

2-ethylbenzo[f][1,7]naphthyridin-5-amine,

2-(3-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine,

8-methylbenzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-phenethylbenzo[f][1,7]naphthyridin-5-amine,

methyl 5-aminobenzo[f][1,7]naphthyridine-3-carboxylate,

(5-aminobenzo[f][1,7]naphthyridin-3-yl)methanol,

benzo[f][1,7]naphthyridin-5-amine,

(5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol,

2-(2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(3-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine,

8-chlorobenzo[f][1,7]naphthyridin-5-amine,

ethyl 5-aminobenzo[f][1,7]naphthyridine-9-carboxylate,

8-methoxybenzo[f][1,7]naphthyridin-5-amine,

8-(trifluoromethyl)benzo[f][1,7]naphthyridin-5-amine,

8-fluorobenzo[f][1,7]naphthyridin-5-amine,

3-methylbenzo[f][1,7]naphthyridin-5-amine,

3-fluorobenzo[f][1,7]naphthyridin-5-amine,

2-phenethylbenzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(2-(naphthalen-1-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(2-(naphthalen-2-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoic acid,

3-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoic acid,

2-(3-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(2-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

(3-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol,

2-(4-chlorophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(4-butylphenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-butylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(4-propylphenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(2,5-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(4-propylphenethyl)benzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(2,4,5-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(2,5-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-isopropylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(4-heptylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(4-isobutoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(4-((2-methoxyethoxy)methoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(4-(2-phenoxyethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(4-(4-phenylbutoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-(allyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(4-(3-phenylpropoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-(heptan-4-yloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(4-(4-methylpent-3-enyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-(2-cyclohexylethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(4-isopropoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(4-(3,3-dimethylbutoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

8-(2-cyclopropylethyl)-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

8-(2-cyclopropylethyl)-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine,

N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide,

N-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetamide,

N-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-4-methylbenzenesulfonamide,

3-methyl-9-p-tolyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzonitrile,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-aminoethyl)-3-methylbenzamide,

8-methyl-2-(2-methyl-4-(1H-tetrazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

methyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoate,

methyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetate,

2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)-4-methylpentanoic acid,

2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamido)acetic acid,

6-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)hexan-1-ol,

7-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)heptanoic acid,

11-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)undecan-1-ol,

ethyl 2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)acetate,

2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)acetic acid,

3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propanoic acid,

6-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)hexanoic acid,

8-methyl-2-(2-methyl-4-(methylthio)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(4-(methylsulfonyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-(hexyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(4-phenethoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(4-(pentyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(4-(4-methylpentyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(2-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(3-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-fluorophenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(2-(thiophen-3-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine,

(5-aminobenzo[f][1,7]naphthyridin-2-yl)methanol,

2-(3,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(3,4-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(3,5-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(2-(benzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(2-nitroethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(aminomethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

N^2,8-dimethylbenzo[f][1,7]naphthyridine-2,5-diamine,

2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-phenylethanol,

2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(4-methoxyphenyl)ethanol,

2-(biphenyl-2-yl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(2-(2,6-dimethylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(2-(5-methoxypyridin-2-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoic acid,

5-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-4-methylpyridin-2(1H)-one,

6-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)pyridin-3-ol

8-methyl-2-(4-(trifluoromethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(2-(2,3-dihydro-1H-inden-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(2-(2,3-dihydro-1H-inden-5-yl)ethyl)benzo[f][1,7]naphthyridin-5-amine,

(E)-3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylic acid,

(E)-ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylate,

(E)-8-(2-cyclopropylvinyl)-2-phenethylbenzo[f][1,7]naphthyridin-5-amine,

8-pentylbenzo[f][1,7]naphthyridin-5-amine,

(E)-8-(2-cyclopropylvinyl)benzo[f][1,7]naphthyridin-5-amine,

8-(2-cyclopropylethyl)-2-phenethylbenzo[f][1,7]naphthyridin-5-amine,

(5-amino-2-phenethylbenzo[f][1,7]naphthyridin-8-yl)methanol,

(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol,

3-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol,

2-(2-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-ethylphenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-ethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-(piperidin-1-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-tert-butylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(4-(piperidin-1-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(3,5-dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(2-(trifluoromethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-hydroxybenzimidamide,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzonitrile,

8-methyl-2-(4-(1-morpholinoethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-aminophenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)guanidine,

8-methyl-2-(4-(1-(phenethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)acetonitrile,

2-(4-(piperidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

1-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)benzyl)piperidin-4-ol,

2-(4-(aminomethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-((ethylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-(2-aminopropan-2-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

1-(1-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid,

8-methyl-2-(4-(1-(phenylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-ethyl-8-methylbenzo[f][1,7]naphthyridin-5-amine,

(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)methanol,

8-methyl-2-propylbenzo[f][1,7]naphthyridin-5-amine,

2-(2-(1H-indol-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(4-ethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(4-phenoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(2,4-dimethylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenol,

2-(2-(2,3-dihydrobenzofuran-5-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,
2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethanol,
3-methyl-9-phenyl-9,10-dihydrobenzo[f]furo[2,3-b][1,7]naphthyridin-6-amine,
8-methylbenzo[f][1,7]naphthyridine-2,5-diamine,
1-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)propan-2-ol,
2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetonitrile,
N-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)acetamide,
2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)-1-(2,4-dimethylphenyl)ethanol,
2-(2-(6-methoxy-4-methylpyridin-3-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,
4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)butan-1-ol,
methyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propanoate,
3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-1-ol,
4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)-2-methylbutan-2-ol,
2-(4-(aminomethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,
(E)-ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)acrylate,
ethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoate,
2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzyl)propane-1,3-diol,
3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propanoic acid,
5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridine-8-carbaldehyde,
ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzoate,
8-methyl-2-(4-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine,
2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)propan-2-ol,
(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)methanol,

ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoic acid,

(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)methanol,

8-methyl-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol,

8-methyl-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine,

(E)-3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)acrylic acid,

ethyl 3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoate,

3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propanoic acid,

3-(5-amino-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-8-yl)propan-1-ol,

5-aminobenzo[f][1,7]naphthyridin-8-ol,

5-aminobenzo[f][1,7]naphthyridine-8-carbaldehyde,

1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanol,

1-(5-aminobenzo[f][1,7]naphthyridin-8-yl)ethanone,

8-isopropylbenzo[f][1,7]naphthyridin-5-amine,

8-vinylbenzo[f][1,7]naphthyridin-5-amine,

8-ethylbenzo[f][1,7]naphthyridin-5-amine,

8-(methoxymethyl)benzo[f][1,7]naphthyridin-5-amine,

(5-amino-2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol,

benzo[f][1,7]naphthyridine-5,8-diamine,

8-(aminomethyl)benzo[f][1,7]naphthyridin-5-amine,

3-fluoro-8-methylbenzo[f][1,7]naphthyridin-5-amine,

(5-amino-3-fluorobenzo[f][1,7]naphthyridin-8-yl)methanol,

3-chlorobenzo[f][1,7]naphthyridine-5,8-diamine,

3-fluorobenzo[f][1,7]naphthyridine-5,8-diamine,

8-isobutylbenzo[f][1,7]naphthyridin-5-amine,

(E)-8-(prop-1-enyl)benzo[f][1,7]naphthyridin-5-amine,

8-propylbenzo[f][1,7]naphthyridin-5-amine,

8-(2-cyclopropylethyl)benzo[f][1,7]naphthyridin-5-amine,

8-phenethylbenzo[f][1,7]naphthyridin-5-amine,

(5-amino-2-(4-bromophenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol,

2-(4-methoxy-2-methylphenethyl)-8-pentylbenzo[f][1,7]naphthyridin-5-amine,

8-(2-cyclopropylethyl)-2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine,

(5-amino-2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol,

(5-amino-2-(4-propoxyphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol,

(2-(2-(1H-indol-5-yl)ethyl)-5-aminobenzo[f][1,7]naphthyridin-8-yl)methanol,

methyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,3-dimethylbenzamide,

N-(2-acetamidoethyl)-4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide,

2-(4-methoxyphenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-methoxy-2-methylphenethyl)benzo[f][1,7]naphthyridin-5-amine,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzamide,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N,N,3-trimethylbenzamide,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-hydroxyethyl)-3-methylbenzamide,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-3-methylbenzamide,

(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(pyrrolidin-1-yl)methanone,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(diethylamino)ethyl)-3-methylbenzamide,

(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(4-ethylpiperazin-1-yl)methanone,

(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)(piperazin-1-yl)methanone,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methyl-N-(2-(pyrrolidin-1-yl)ethyl)benzamide,

4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N,3-dimethylbenzamide,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-N-(2-(dimethylamino)ethyl)-N-methylbenzamide,

2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol,

2-(4-butoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(2-(biphenyl-4-yl)ethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-((1,3-dihydroisobenzofuran-1-yl)methyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(4-(2-methylallyloxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-(isopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl propyl carbonate,

ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoate,

2-(4-(cyclopentyloxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(4-(cyclobutylmethoxy)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

8-methyl-2-(4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-1-phenylethanone,

5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)pentanoic acid,

2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)ethanol,

2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)-N,N-dimethylacetamide,

8-methyl-2-(2-methyl-4-(2-morpholinoethoxy)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethanol,

diethyl 3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonate,

3-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)propylphosphonic acid,

2-(4-butoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol,

2-(2-(4-(2-(5-aminobenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethanol,

ethyl 5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoate,

5-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)pentanoic acid,

2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethanol,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl ethyl carbonate,

methyl 4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoate,

4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenoxy)butanoic acid,

4-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)butanoic acid,

2-(4-(isopentyloxy)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl hexyl carbonate,

2-(2,4,6-trimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine,

(5-amino-2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol,

diethyl 3-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)propylphosphonate,

diethyl 3-(2-(2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenoxy)ethoxy)ethoxy)propylphosphonate,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl dimethylsulfamate,

(5-amino-2-(4-(dimethylamino)phenethyl)benzo[f][1,7]naphthyridin-8-yl)methanol,

2-(4-(dimethylamino)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenol,

1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone,

2-(4-((dimethylamino)methyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(4-(1-(dimethylamino)ethyl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanone oxime,

8-methyl-2-(4-((methylamino)methyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)benzylamino)ethanol,

8-methyl-2-(4-(pyrrolidin-1-ylmethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

2-(3,4-dimethoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)ethanol,

1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethanol,

8-methyl-2-(4-(oxazol-5-yl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propanenitrile,

(2R)-2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propan-1-ol,

8-methyl-2-(4-(1-(piperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

((2S)-1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidin-2-yl)methanol,

N^1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^2,N^2-dimethylethane-1,2-diamine,

3-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)propanoic acid,

8-methyl-2-(4-(1-(4-methylpiperazin-1-yl)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

N^2-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^1,N^1-dimethylpropane-1,2-diamine,

8-methyl-2-(4-(1-(2-(pyridin-4-yl)ethylamino)ethyl)phenethyl)benzo[f][1,7]naphthyridin-5-amine,

N^1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)-N^2,N^2-diethylethane-1,2-diamine,

2-(4-(dimethylamino)-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine,

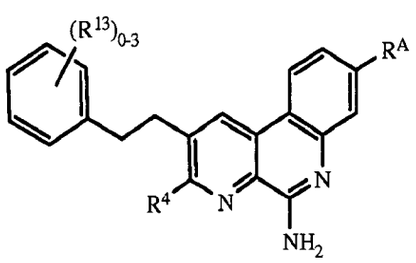
1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethyl)pyrrolidine-3-carboxylic acid,

4-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)phenyl)ethylamino)phenol,

1-(1-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2 yl)ethyl)phenyl)ethyl)pyrrolidin-3-ol, and

2-(4-(2-aminopropan-2-yl)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine.

22. A compound of formula (XVI)



(XVI)

wherein each R^4, R^A and R^{13} is independently selected from H, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH_2OH$, $-OCH_3$, $-COOCH_3$, $-COOCH_2CH_3$, F, Cl, Br, $-CH_2OCH_3$, $CH_2OCH_2CH_3$, $-N(CH_3)_2$, $-((O(CH_2)_2)_{2-4}OH$, $-O(CH_2)_{2-4}-OH$, $-O(CH_2)_{2-4}-(PO_3H_2)$, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}-CH(CH_3)_2$, C_2-C_6 alkyl substituted with 1-3 substituents selected from –OH, $-CH_3$, cyclopropyl, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}(PO_3H_2)$, -COOH, $COOCH_3$, and $-COOCH_2CH_3$;

or a pharmaceutically acceptable salt thereof.

23. The compound of claim 22, wherein R^4 is H.

24. The compound of claim 22 or claim 23, having one to three R^{13} groups.

25. The compound of any one of claims 22-24, wherein R^A is H or $-CH_3$.

26. The compound of any one of claims 22-25, having two R^{13} groups selected from the group consisting of $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH_2OH$, $-OCH_3$, $-COOCH_3$, $-COOCH_2CH_3$, F, Cl, Br, $-CH_2OCH_3$, $CH_2OCH_2CH_3$, $-N(CH_3)_2$, $-((O(CH_2)_2)_{2-4}OH$, $-O(CH_2)_{2-4}-OH$, $-O(CH_2)_{2-4}-(PO_3H_2)$, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}-CH(CH_3)_2$, C_2-C_6 alkyl substituted with 1-3 substituents selected from $-OH$, $-CH_3$, cyclopropyl, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}(PO_3H_2)$, -COOH, $COOCH_3$, and $-COOCH_2CH_3$.

27. The compound of claim 22 selected from:

2-(4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylphenyl)propan-2-ol;

2-(4-methoxy-2-methylphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine;

2-(2,4-dimethylphenethyl)benzo[f][1,7]naphthyridin-5-amine;

ethyl 4-(2-(5-amino-8-methylbenzo[f][1,7]naphthyridin-2-yl)ethyl)-3-methylbenzoate;

2-(4-(dimethylamino)phenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine, and

2-(4-methoxyphenethyl)-8-methylbenzo[f][1,7]naphthyridin-5-amine.

28. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any of claims 1-27 and a pharmaceutically acceptable carrier.

29. A medicament for treating a disease or disorder where modulation of a TLR receptor is implicated, wherein the medicament comprises a therapeutically effective amount of a compound of any of claims 1-27.

30. The medicament of claim 29, wherein the TLR receptor is TLR7.

31. The medicament of claim 29, wherein the TLR receptor is TLR8.

32. The medicament of claim 29, wherein the compound is a TLR agonist.

33. The medicament of claim 30, wherein the compound is a TLR7 agonist.

34. The medicament of claim 31, wherein the compound is a TLR8 agonist.

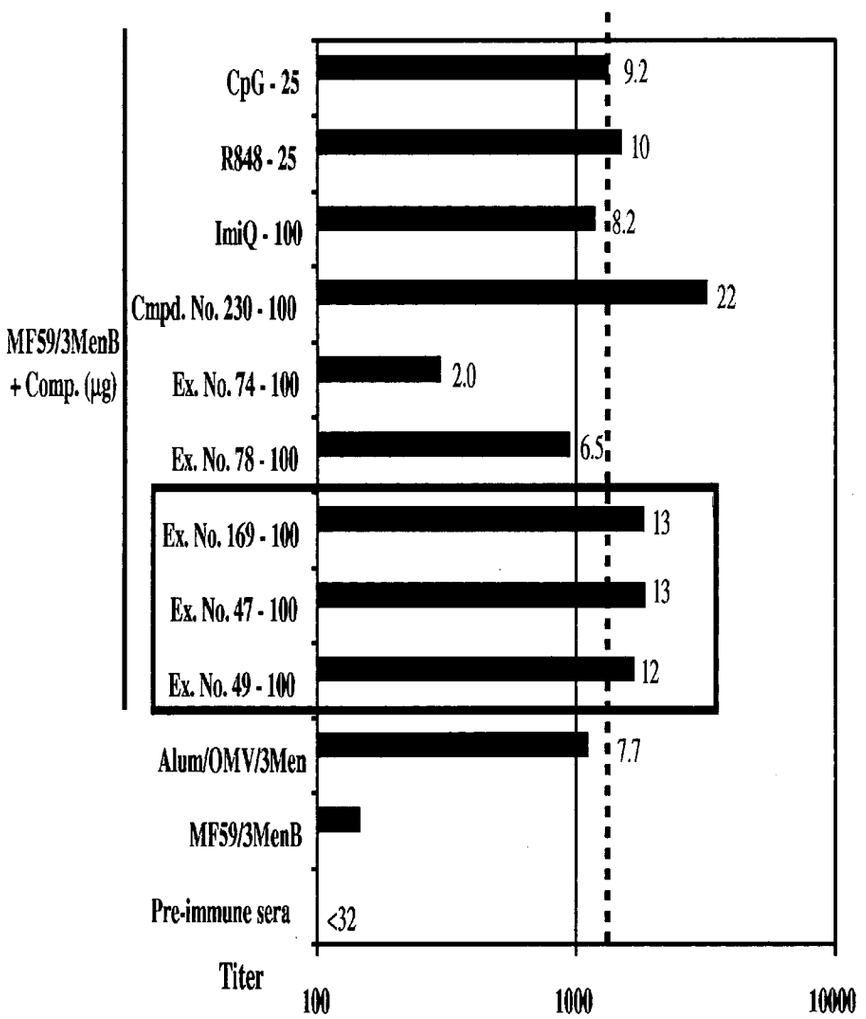
35. Use of a compound of any of claims 1-27 in the manufacture of a medicament for treating a disease or disorder in a patient where modulation of a TLR receptor is implicated.

36. A method for modulating a TLR, comprising administering to a system or a subject in need thereof, a therapeutically effective amount of a compound any of claims 1-27, or pharmaceutically acceptable salts or pharmaceutical compositions thereof, thereby modulating the TLR.
37. A method for treating a disease or disorder where modulation of TLR receptor is implicated, comprising administering to a system or subject in need of such treatment an effective amount of a compound of any of claims 1-27, or pharmaceutically acceptable salts or pharmaceutical compositions thereof, thereby treating the disease or disorder.
38. The method of claim 36 or claim 37, wherein the TLR is TLR7.
39. The method of claim 36 or claim 37, wherein the TLR is TLR8.
40. The method of claim 36 or claim 37, wherein the compound is a TLR agonist.
41. The method of claim 36 or claim 37, wherein the compound is a TLR7 agonist.
42. The method of claim 36 or claim 37, wherein the compound is a TLR8 agonist.
43. The method of any of claims 36-42, comprising administering the compound to a cell or tissue system or to a human or animal subject.
44. The method of claim 37, wherein the disease or condition is an infectious disease, an inflammatory disease, a respiratory disease, a dermatological disease or an autoimmune disease.
45. The method of claim 44, wherein the disease or condition is asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohns disease, bronchitis, dermatitis, actinic keratosis, basal cell carcinoma, allergic rhinitis, psoriasis, scleroderma, urticaria, rheumatoid arthritis, multiple sclerosis, cancer, breast cancer, HIV or lupus.
46. A method for treating a cell-proliferative condition, comprising administering to a system or subject in need of such treatment an effective amount of a compound of any of claims 1-27, or pharmaceutically acceptable salts or pharmaceutical compositions thereof; wherein the cell-proliferative condition is lymphoma, osteosarcoma, melanoma, or a tumor of breast, renal, prostate, colorectal, thyroid, ovarian, pancreatic, neuronal, lung, uterine or gastrointestinal tumor.
47. A pharmaceutical composition comprising a compound of any of claims 1-27, an antigen and a pharmaceutically acceptable carrier, wherein the pharmaceutical

composition is an immunogenic composition and the compound is an immune potentiator.

48. The pharmaceutical composition of claim 47, wherein the pharmaceutical composition further comprises an additional immunoregulatory agent.
49. The pharmaceutical composition of claim 47, wherein the additional immunoregulatory agent is an adjuvant selected from a mineral-containing composition, an oil emulsion, a saponin formulation, a virosome, a virus-like particle, a bacterial derivative, a microbial derivative, a human immunomodulator, a bioadhesive, a mucoadhesive, a microparticle, a liposome, a polyoxyethylene ether formulation, a polyoxyethylene ester formulation, a polyphosphazene, a muramyl peptide, or an imidazoquinolone compounds.
50. The pharmaceutical composition of claim 49, wherein the adjuvant is an oil emulsion.
51. The pharmaceutical composition of any of claims 47-50, wherein the compound is present in an amount sufficient to produce an immunostimulatory effect when administered.
52. A method for enhancing the effectiveness of an immunogenic composition, comprising adding an effective amount of a compound according to one of claims 1-27 to the immunogenic composition.
53. An immunogenic composition comprising a compound of any one of claims 22-27, and an antigen, wherein the amount of the compound is an amount effective to enhance an immune response to the antigen in a subject to whom the composition is administered.
54. The immunogenic composition of claim 53, wherein the antigen is a bacterial antigen.
55. The immunogenic composition of claim 54, wherein the bacterial antigen is an antigen of a strain of *Neisseria meningitides*.
56. The immunogenic composition of claim 53, wherein the antigen is a viral antigen or a fungal antigen.
57. The immunogenic composition of claim 53, further comprising an additional adjuvant.

FIGURE 1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ImiQ - 100
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Ex. No. 169 - 100
Ex. No. 47 - 100
Ex. No. 49 - 100
Alum/OMV/3Men
MF59/3MenB
Pre-immune sera
9.2
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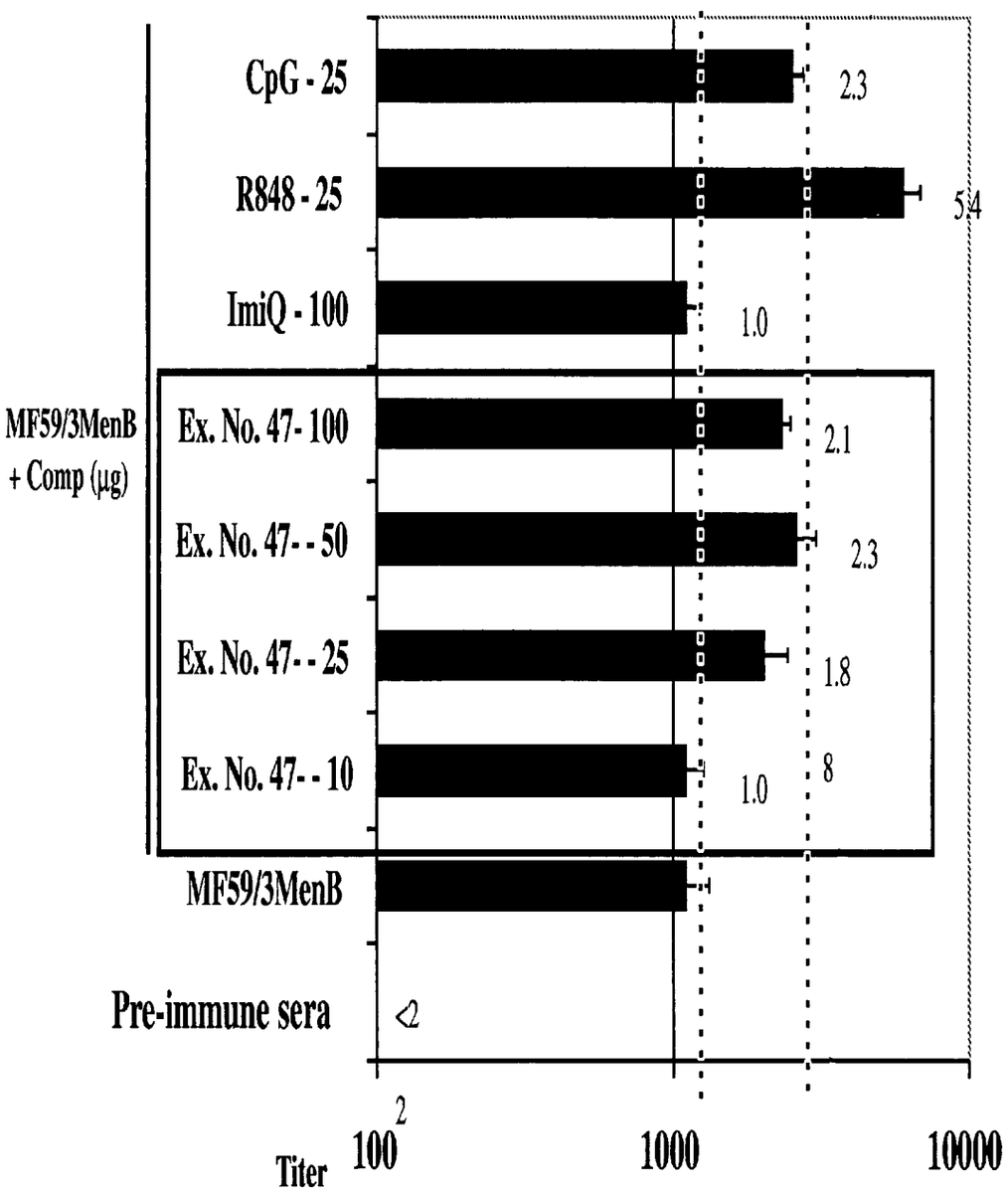
8.2
22
2.0
6.5
13
13
12
7.7
<32
Titer
100
1000
10000

FIGURE 2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2.3
R848 - 25
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ImiQ - 100
1.0
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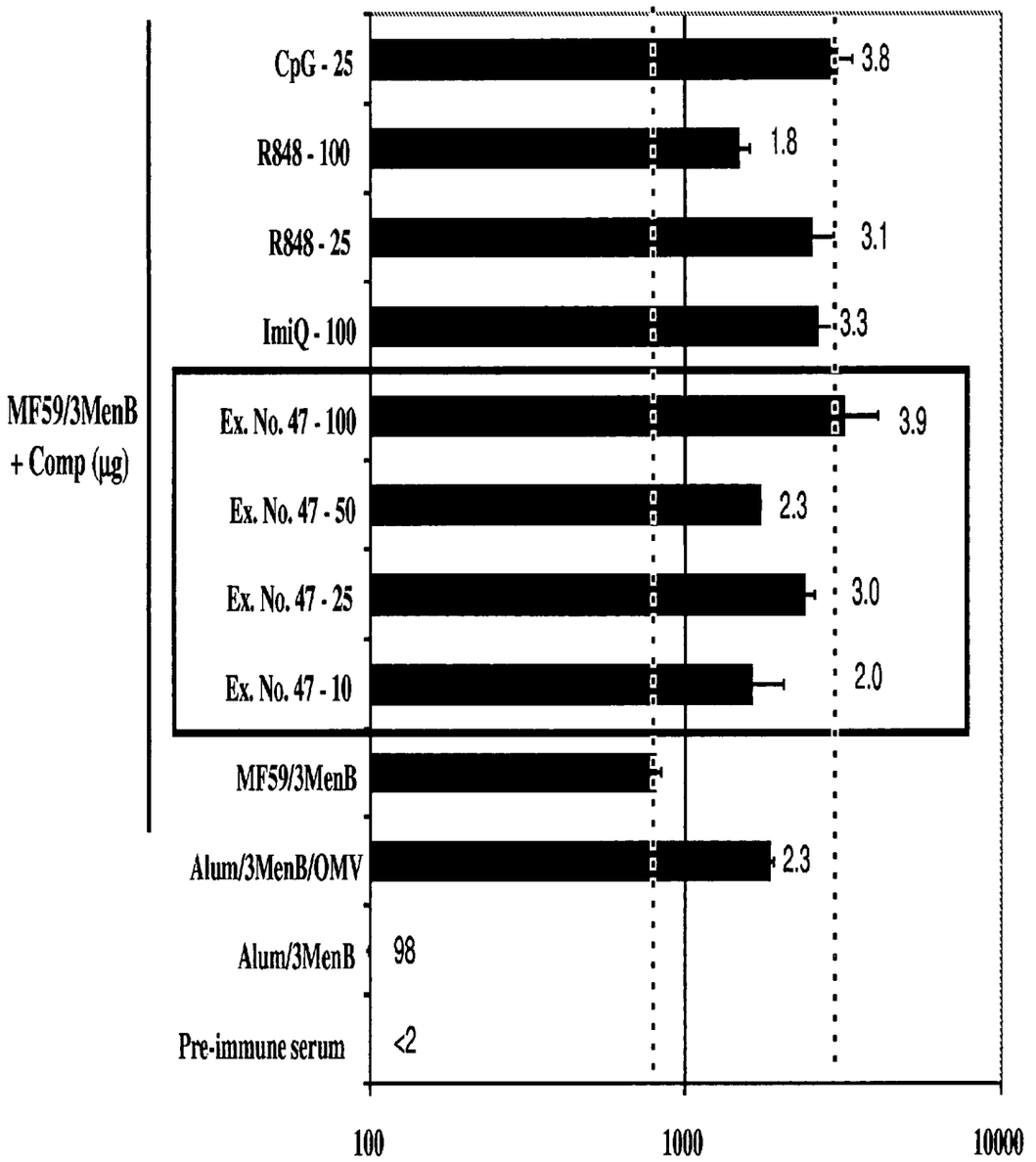
Ex. No. 47- 100
2.1
Ex. No. 47- - 50
2.3
Ex. No. 47- - 25
1.8
Ex. No. 47- - 10
1.0
8
MF59/3MenB
Pre-immune sera
<2
Titer
100
2
1000
10000

FIGURE 3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+ Comp (µg)
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R848 - 100
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ImiQ - 100
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Ex. No. 47 - 25
Ex. No. 47 - 10
MF59/3MenB
Alum/3MenB/OMV
Alum/3MenB
Pre-immune serum
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1.8
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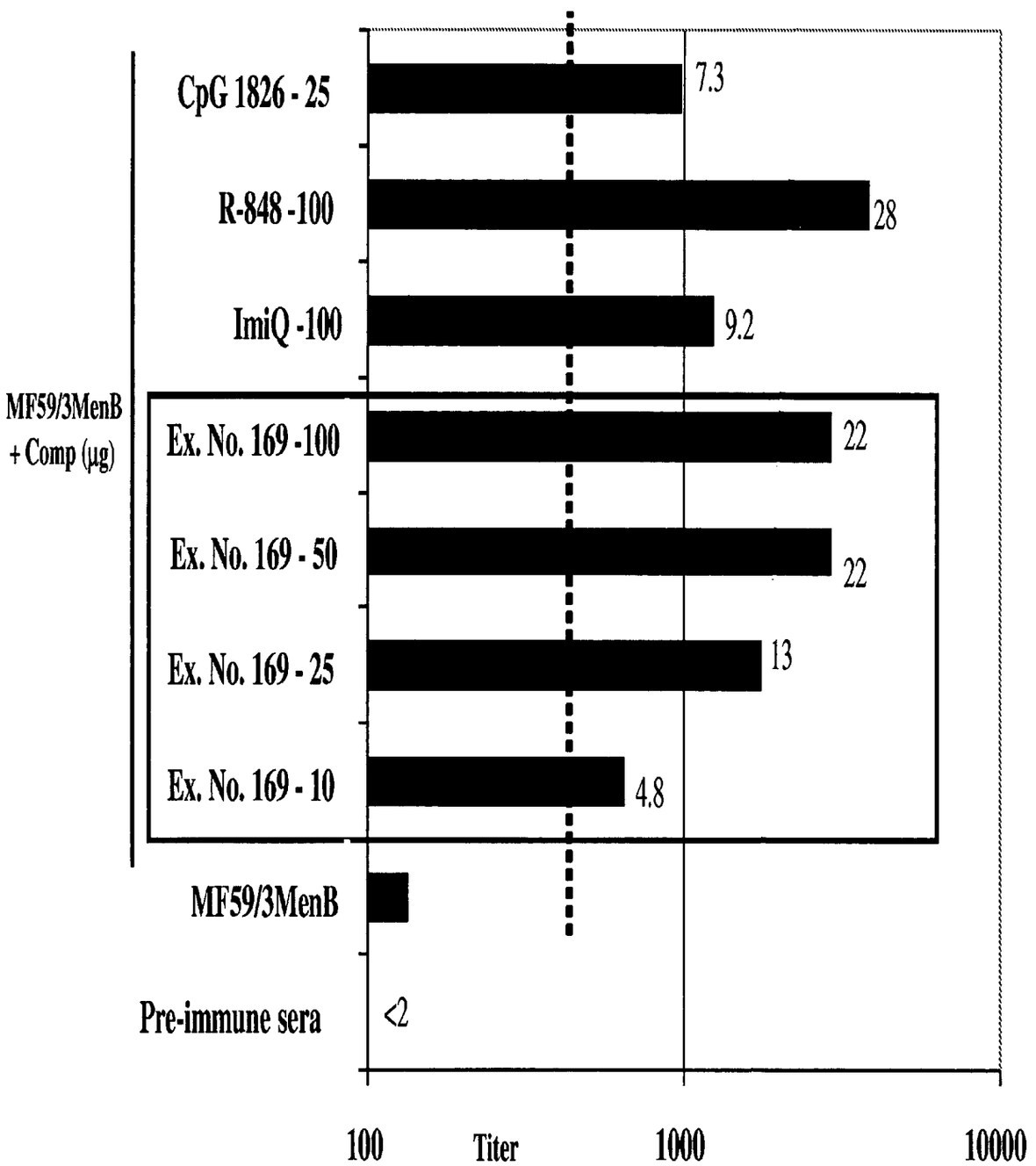
FIGURE 4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R-848 -100
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ImiQ -100
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MF59/3MenB + Comp (μg)
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Ex. No. 169 - 50
22
Ex. No. 169 - 25
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Pre-immune sera
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Titer
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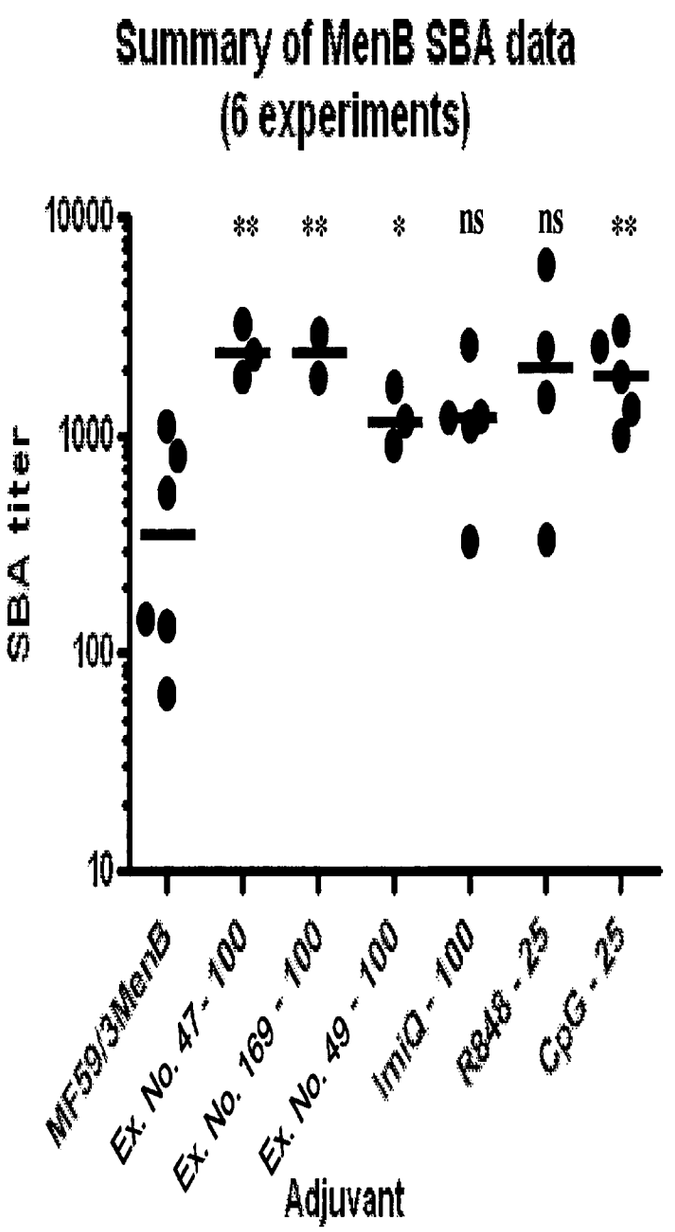
FIGURE 5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Ex. No. 169 - 100
Ex. No. 49 - 100
ImiQ - 100
R848 - 25
CpG - 25
Adjuvant

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/035563

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D221/12 C07D471/04 C07D471/12 C07D491/056 C07D491/12
C07D495/04 A61K31/4375 A61P37/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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, BIOSIS, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 741 909 A (GERSTER JOHN F [US] ET AL) 21 April 1998 (1998-04-21) column 2; compound I column 11, lines 38-65	1-59
A	WO 2007/109813 A (NOVARTIS AG [CH]; SUTTON JAMES [US]; XU FENG [US]; VALIANTE NICHOLAS [) 27 September 2007 (2007-09-27) claims 1,25-39,57	1-59

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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
9 June 2009	30/06/2009

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, Fax: (+31-70) 340-3016	Gutke, Hans-Jürgen

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/035563

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FERRARIS DANA ET AL:· "Design and synthesis of poly ADP-ribose polymerase-1 inhibitors. 2. Biological evaluation of aza-5(H)-phenanthridin-6-ones as potent, aqueous-soluble compounds for the treatment of ischemic injuries." JOURNAL OF MEDICINAL CHEMISTRY, vol. 46, no. 14, 3 July 2003 (2003-07-03), pages 3138-3151, XP002531095 ISSN: 0022-2623 page 3139; compound 12 ------	1,3,4, 7-11,13, 14,16-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/035563

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5741909 A	21-04-1998	NONE	
WO 2007109813 A	27-09-2007	CA 2646539 A1	27-09-2007
		EP 2010537 A1	07-01-2009

SEQUENCE LISTING

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Cortez, Alex

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Lys Asn Asp Lys Ile Ser Arg Phe Asp Phe Val Gln Lys Ile Glu Val
65                  70                  75                  80

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<400> 4

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35 40 45

Asp Met Ala Ala Val Ser Glu Glu Asn Thr Gly Asn Gly Gly Ala Ala
50 55 60

Ala Thr Asp Lys Pro Lys Asn Glu Asp Glu Gly Ala Gln Asn Asp Met
65 70 75 80

Pro Gln Asn Ala Ala Asp Thr Asp Ser Leu Thr Pro Asn His Thr Pro
85 90 95

Ala Ser Asn Met Pro Ala Gly Asn Met Glu Asn Gln Ala Pro Asp Ala
100 105 110

Gly Glu Ser Glu Gln Pro Ala Asn Gln Pro Asp Met Ala Asn Thr Ala
115 120 125

Asp Gly Met Gln Gly Asp Asp Pro Ser Ala Gly Gly Glu Asn Ala Gly
130 135 140

Asn Thr Ala Ala Gln Gly Thr Asn Gln Ala Glu Asn Asn Gln Thr Ala
145 150 155 160

Gly Ser Gln Asn Pro Ala Ser Ser Thr Asn Pro Ser Ala Thr Asn Ser
165 170 175

Gly Gly Asp Phe Gly Arg Thr Asn Val Gly Asn Ser Val Val Ile Asp
180 185 190

Gly Pro Ser Gln Asn Ile Thr Leu Thr His Cys Lys Gly Asp Ser Cys
195 200 205

Ser Gly Asn Asn Phe Leu Asp Glu Glu Val Gln Leu Lys Ser Glu Phe
210 215 220

Glu Lys Leu Ser Asp Ala Asp Lys Ile Ser Asn Tyr Lys Lys Asp Gly
225 230 235 240

Lys Asn Asp Gly Lys Asn Asp Lys Phe Val Gly Leu Val Ala Asp Ser
245 250 255

Val Gln Met Lys Gly Ile Asn Gln Tyr Ile Ile Phe Tyr Lys Pro Lys
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Pro Thr Ser Phe Ala Arg Phe Arg Arg Ser Ala Arg Ser Arg Arg Ser
275 280 285

Leu Pro Ala Glu Met Pro Leu Ile Pro Val Asn Gln Ala Asp Thr Leu
290 295 300

Ile Val Asp Gly Glu Ala Val Ser Leu Thr Gly His Ser Gly Asn Ile
305 310 315 320

Phe Ala Pro Glu Gly Asn Tyr Arg Tyr Leu Thr Tyr Gly Ala Glu Lys
325 330 335

Leu Pro Gly Gly Ser Tyr Ala Leu Arg Val Gln Gly Glu Pro Ser Lys
340 345 350

Gly Glu Met Leu Ala Gly Thr Ala Val Tyr Asn Gly Glu Val Leu His
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Phe His Thr Glu Asn Gly Arg Pro Ser Pro Ser Arg Gly Arg Phe Ala
370 375 380

Ala Lys Val Asp Phe Gly Ser Lys Ser Val Asp Gly Ile Ile Asp Ser
385 390 395 400

Gly Asp Gly Leu His Met Gly Thr Gln Lys Phe Lys Ala Ala Ile Asp
405 410 415

Gly Asn Gly Phe Lys Gly Thr Trp Thr Glu Asn Gly Gly Gly Asp Val
420 425 430

Ser Gly Lys Phe Tyr Gly Pro Ala Gly Glu Glu Val Ala Gly Lys Tyr
435 440 445

Ser Tyr Arg Pro Thr Asp Ala Glu Lys Gly Gly Phe Gly Val Phe Ala
450 455 460

Gly Lys Lys Glu Gln Asp Gly Ser Gly Gly Gly Gly Ala Thr Tyr Lys
465 470 475 480

Val Asp Glu Tyr His Ala Asn Ala Arg Phe Ala Ile Asp His Phe Asn
485 490 495

Thr Ser Thr Asn Val Gly Gly Phe Tyr Gly Leu Thr Gly Ser Val Glu
500 505 510

Phe Asp Gln Ala Lys Arg Asp Gly Lys Ile Asp Ile Thr Ile Pro Val
515 520 525

Ala Asn Leu Gln Ser Gly Ser Gln His Phe Thr Asp His Leu Lys Ser
530 535 540

Ala Asp Ile Phe Asp Ala Ala Gln Tyr Pro Asp Ile Arg Phe Val Ser
545 550 555 560

Thr Lys Phe Asn Phe Asn Gly Lys Lys Leu Val Ser Val Asp Gly Asn
565 570 575

Leu Thr Met His Gly Lys Thr Ala Pro Val Lys Leu Lys Ala Glu Lys

580 585 590

Phe Asn Cys Tyr Gln Ser Pro Met Ala Lys Thr Glu Val Cys Gly Gly
595 600 605

Asp Phe Ser Thr Thr Ile Asp Arg Thr Lys Trp Gly Val Asp Tyr Leu
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Ala Ala Lys Gln

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<400> 5

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Thr Lys Gly Tyr Thr Pro Gln Ile Ser Val Val Gly Tyr Asn Arg His
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Leu Leu Leu Leu Gly Gln Val Ala Thr Glu Gly Glu Lys Gln Phe Val
65 70 75 80

Gly Gln Ile Ala Arg Ser Glu Gln Ala Ala Glu Gly Val Tyr Asn Tyr
85 90 95

Ile Thr Val Ala Ser Leu Pro Arg Thr Ala Gly Asp Ile Ala Gly Asp
100 105 110

Thr Trp Asn Thr Ser Lys Val Arg Ala Thr Leu Leu Gly Ile Ser Pro
115 120 125

Ala Thr Gln Ala Arg Val Lys Ile Val Thr Tyr Gly Asn Val Thr Tyr
130 135 140

Val Met Gly Ile Leu Thr Pro Glu Glu Gln Ala Gln Ile Thr Gln Lys

145 150 155 160

Val Ser Thr Thr Val Gly Val Gln Lys Val Ile Thr Leu Tyr Gln Asn
165 170 175

Tyr Val Gln Arg Gly Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly
180 185 190

Ala Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys
195 200 205

Gly Leu Gln Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys
210 215 220

Leu Lys Leu Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp
225 230 235 240

Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp
245 250 255

Phe Ile Arg Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser
260 265 270

Gly Glu Phe Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Phe
275 280 285

Gln Thr Glu Gln Ile Gln Asp Ser Glu His Ser Gly Lys Met Val Ala
290 295 300

Lys Arg Gln Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe
305 310 315 320

Asp Lys Leu Pro Glu Gly Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe
325 330 335

Gly Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala
340 345 350

Ala Lys Gln Gly Asn Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu
355 360 365

Asn Val Asp Leu Ala Ala Ala Asp Ile Lys Pro Asp Gly Lys Arg His
370 375 380

Ala Val Ile Ser Gly Ser Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser
385 390 395 400

Tyr Ser Leu Gly Ile Phe Gly Gly Lys Ala Gln Glu Val Ala Gly Ser
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Lys Gln

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<213> Neisseria meningitidis

<400> 6

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Ala Ala Tyr Asn Asn Gly Gln Glu Ile Asn Gly Phe Lys Ala Gly Glu
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Thr Ile Tyr Asp Ile Asp Glu Asp Gly Thr Ile Thr Lys Lys Asp Ala
35 40 45

Thr Ala Ala Asp Val Glu Ala Asp Asp Phe Lys Gly Leu Gly Leu Lys
50 55 60

Lys Val Val Thr Asn Leu Thr Lys Thr Val Asn Glu Asn Lys Gln Asn
65 70 75 80

Val Asp Ala Lys Val Lys Ala Ala Glu Ser Glu Ile Glu Lys Leu Thr
85 90 95

Thr Lys Leu Ala Asp Thr Asp Ala Ala Leu Ala Asp Thr Asp Ala Ala
100 105 110

Leu Asp Ala Thr Thr Asn Ala Leu Asn Lys Leu Gly Glu Asn Ile Thr
115 120 125

Thr Phe Ala Glu Glu Thr Lys Thr Asn Ile Val Lys Ile Asp Glu Lys
130 135 140

Leu Glu Ala Val Ala Asp Thr Val Asp Lys His Ala Glu Ala Phe Asn
145 150 155 160

Asp Ile Ala Asp Ser Leu Asp Glu Thr Asn Thr Lys Ala Asp Glu Ala
165 170 175

Val Lys Thr Ala Asn Glu Ala Lys Gln Thr Ala Glu Glu Thr Lys Gln
180 185 190

Asn Val Asp Ala Lys Val Lys Ala Ala Glu Thr Ala Ala Gly Lys Ala
195 200 205

Glu Ala Ala Ala Gly Thr Ala Asn Thr Ala Ala Asp Lys Ala Glu Ala
210 215 220

Val Ala Ala Lys Val Thr Asp Ile Lys Ala Asp Ile Ala Thr Asn Lys
225 230 235 240

Asp Asn Ile Ala Lys Lys Ala Asn Ser Ala Asp Val Tyr Thr Arg Glu
245 250 255

Glu Ser Asp Ser Lys Phe Val Arg Ile Asp Gly Leu Asn Ala Thr Thr
260 265 270

Glu Lys Leu Asp Thr Arg Leu Ala Ser Ala Glu Lys Ser Ile Ala Asp
275 280 285

His Asp Thr Arg Leu Asn Gly Leu Asp Lys Thr Val Ser Asp Leu Arg
290 295 300

Lys Glu Thr Arg Gln Gly Leu Ala Glu Gln Ala Ala Leu Ser Gly Leu
305 310 315 320

Phe Gln Pro Tyr Asn Val Gly
325

COMPUESTOS Y COMPOSICIONES COMO MODULADORES DE LA ACTIVIDAD DE TLR, UN MEDICAMENTO, MÉTODO PARA TRATAR UNA ENFERMEDAD, Y COMPOSICIONES INMUNOGÉNICAS

REFERENCIA A SOLICITUDES RELACIONADAS.

Esta solicitud reivindica el beneficio de prioridad conforme al Título 35 U. S. C. § 119 (e), de la Solicitud de Patente Provisional de los Estados Unidos Nro. 61/033.139, presentada el 3 de marzo de 2008, y de la Solicitud de Patente Provisional de los Estados Unidos Nro. 61/148.336, presentada el 29 de enero de 2009. La revelación de las solicitudes de prioridad se incorpora en la presente solicitud a modo de referencia, en su totalidad y para todos los propósitos.

DECLARACIÓN DE APOYO GUBERNAMENTAL.

Esta invención se hizo posible, en parte, con el apoyo gubernamental conforme a DTRA Concesión Nro. HDTRA1–07–9–0001 otorgada por el Departamento de Defensa. El gobierno posee ciertos derechos sobre la invención.

CAMPO DE LA INVENCIÓN.

La invención se refiere a moduladores de receptores de tipo Toll (TLR, por sus siglas en inglés) y a métodos de uso de dichos compuestos.

ANTECEDENTES DE LA INVENCIÓN.

La detección temprana de clases específicas de patógenos es lograda por el sistema inmunitario innato, con la ayuda de receptores de reconocimiento de patrones (PRR, por sus siglas en inglés). Los patógenos detectados incluyen virus, bacterias, protozoos y hongos, y cada uno de estos expresa constitutivamente un grupo de moléculas resistentes a la mutación, específicas de clase, denominadas patrones moleculares asociados con patógenos (PAMP, por

sus siglas en inglés). Estos marcadores moleculares pueden estar compuestos por proteínas, carbohidratos, lípidos, ácidos nucleicos o sus combinaciones, y pueden ubicarse interna o externamente. Ejemplos de PAMP incluyen carbohidratos bacterianos (lipopolisacárido o LPS, manosa), ácidos nucleicos (ARN o ADN bacteriano o viral), peptidoglicanos y ácidos lipotecoicos (de bacterias Gram positivas); *N*–formilmetionina, lipoproteínas y glucanos fúngicos.

Los receptores de reconocimiento de patrones han evolucionado para sacar provecho de tres cualidades de los PAMP. En primer lugar, la expresión constitutiva permite al huésped la detección del patógeno, sin consideración de su etapa de ciclo de vida. En segundo lugar, los PAMP son específicos de clase, lo que permite al huésped la distinción entre patógenos y, de ese modo, la adaptación de su respuesta. En tercer lugar, la resistencia a la mutación permite al huésped el reconocimiento del patógeno, sin consideración de su cepa particular.

Los receptores de reconocimiento de patrones participan en más de una función, además, de solo el reconocimiento de patógenos por medio de los PAMP. Una vez ligados, los receptores de reconocimiento de patrones tienden a agruparse, a reclutar otras proteínas extracelulares e intracelulares en el complejo, e iniciar cascadas de señalización que, en última instancia, afectan la transcripción. Asimismo, los receptores de reconocimiento de patrones participan en la activación de funciones de complemento, coagulación, fagocitosis, inflamación y apoptosis, en respuesta a la detección de patógenos.

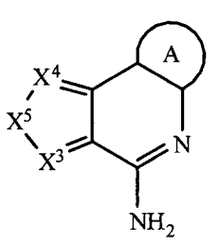
Los receptores de reconocimiento de patrones (PRR) pueden dividirse en PRR endocíticos o PRR de señalización. Los PRR de señalización incluyen las grandes familias de receptores de tipo Toll ligados a membrana (TLR, por sus siglas en inglés) y receptores de tipo NOD citoplásmicos, mientras que los PRR endocíticos promueven la adhesión, la absorción y la destrucción de

microorganismos por fagocitos, sin transmitir una señal intracelular; se hallan en todos los fagocitos y median en la remoción de células apoptóticas. Además, los PRR endocíticos reconocen carbohidratos e incluyen receptores de manosa de macrófagos, receptores de glucano presentes en todos los fagocitos y receptores depuradores que reconocen ligandos cargados.

SÍNTESIS DE LA INVENCIÓN.

En la presente solicitud, se proveen compuestos y sus composiciones farmacéuticas, que son útiles moduladores de receptores de tipo toll.

En un aspecto, se proveen en esta solicitud dichos compuestos y sus sales aceptables para uso farmacéutico, solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), derivados de N–óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezclas de sus isómeros, que tienen una estructura de acuerdo con la Fórmula (I), como se describe en la presente solicitud. Ciertas realizaciones de la invención incluyen compuestos de la Fórmula (I–A), métodos para su uso y composiciones farmacéuticas que comprenden estos compuestos:



Fórmula (I–A)

donde:

X^3 es N; X^4 es N o CR^3, y X^5 es $–CR^4=CR^5–$;

R^1 y R^2 son H; R^3 es H;

R^4 y R^5 se selecciona, de manera independiente, de H, halógeno, $–C(O)OR^7$, $–C(O)R^7$, $–C(O)N(R^{11}R^{12})$, $–N(R^{11}R^{12})$, $–N(R^9)_2$, $–NHN(R^9)_2$, $–SR^7$,

$-(CH_2)_nOR^7$, $-(CH_2)_nR^7$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, -alquilo-C_1-C_6, heteroalquilo C_1-C_6, haloalquilo C_1-C_6, alqueno C_2-C_8, alquino C_2-C_8, alcoxi C_1-C_6, haloalcoxi C_1-C_6, arilo, heteroarilo, cicloalquilo C_3-C_8 y heterocicloalquilo C_3-C_8, donde los grupos alquilo C_1-C_6, heteroalquilo C_1-C_6, haloalquilo C_1-C_6, alqueno C_2-C_8, alquino C_2-C_8, alcoxi C_1-C_6, haloalcoxi C_1-C_6, arilo, heteroarilo, cicloalquilo C_3-C_8 y heterocicloalquilo C_3-C_8 de R^4 y R^5 están, de modo independiente, opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de manera independiente de halógeno, -CN, $-NO_2$, $-R^7$, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-C(O)N(R^9)_2$, $-S(O)_2R^8$, $-S(O)_2\ N(R^9)_2$ y $-NR^9S(O)_2R^8$; o R^3 y R^4, o R^4 y R^5, cuando se presentan en átomos de anillos adyacentes, pueden estar, en forma opcional, ligados para formar un anillo de 5 a 6 miembros, donde el anillo de 5-6 miembros está opcionalmente sustituido con R^7;

cada L se selecciona de manera independiente de un enlace, $-(O(CH_2)_m)_t-$, alquilo C_1-C_6, alquenileno C_2-C_6 y alquinileno C_2-C_6, donde los alquilo C_1-C_6, alquenileno C_2-C_6 y alquinileno C_2-C_6 de L están, cada uno, opcionalmente sustituidos con 1 a 4 sustituyentes seleccionados independientemente de halógeno, $-R^8$, $-OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, y $-OP(O)(OR^{10})_2$;

R^7 se selecciona de H, alquilo C_1-C_6, arilo, heteroarilo, cicloalquilo C_3-C_8, heteroalquilo C_1-C_6, haloalquilo C_1-C_6, alqueno C_2-C_8, alquino C_2-C_8, alcoxi C_1-C_6, haloalcoxi C_1-C_6, heteroarilo y heterocicloalquilo C_3-C_8, donde los grupos alquilo C_1-C_6, arilo, heteroarilo, cicloalquilo C_3-C_8, heteroalquilo C_1-C_6, haloalquilo C_1-C_6, alqueno C_2-C_8, alquino C_2-C_8, alcoxi C_1-C_6, haloalcoxi C_1-C_6, heteroarilo y heterocicloalquilo C_3-C_8 de R^7 están, de manera independiente, opcionalmente sustituidos con 1 a 3 grupos R^{13}, y cada R^{13} se selecciona de manera independiente de halógeno, -CN, $-LR^9$, $-LOR^9$, $-OLR^9$, $-LR^{10}$, $-LOR^{10}$,

$-OLR^{10}$, $-LR^8$, $-LOR^8$, $-OLR^8$, $-LSR^8$, $-LSR^{10}$, $-LC(O)R^8$, $-OLC(O)R^8$, $-LC(O)OR^8$, $-LC(O)R^{10}$, $-LOC(O)OR^8$, $-LC(O)NR^9R^{11}$, $-LC(O)NR^9R^8$, $-LN(R^9)_2$, $-LNR^9R^8$, $-LNR^9R^{10}$, $-LC(O)N(R^9)_2$, $-LS(O)_2R^8$, $-LS(O)R^8$, $-LC(O)NR^8OH$, $-LNR^9C(O)R^8$, $-LNR^9C(O)OR^8$, $-LS(O)_2N(R^9)_2$, $-OLS(O)_2N(R^9)_2$, $-LNR^9S(O)_2R^8$, $-LC(O)NR^9LN(R^9)_2$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$ y $-OLP(O)(OR^{10})$;

cada R^8 se selecciona de modo independiente de H, $-CH(R^{10})_2$, alquilo C_1–C_8, alqueno C_2–C_8, alquino C_2–C_8, haloalquilo C_1–C_6, alcoxi C_1–C_6, heteroalquilo C_1–C_6, cicloalquilo C_3–C_8, heterocicloalquilo C_2–C_8, hidroxialquilo C_1–C_6 y haloalcoxi C_1–C_6, donde los grupos alquilo C_1–C_8, alqueno C_2–C_8, alquino C_2–C_8, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alcoxi C_1–C_6, cicloalquilo C_3–C_8, heterocicloalquilo C_2–C_8, hidroxialquilo C_1–C_6 y haloalcoxi C_1–C_6 de R^8 están, cada uno, opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente de –CN, R^{11}, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-OC(O)R^{11}$, $-C(O)N(R^9)_2$, $-C(O)OR^{11}$, $-NR^9C(O)R^{11}$, $-NR^9R^{10}$, $-NR^{11}R^{12}$, $-N(R^9)_2$, $-OR^9$, $-OR^{10}$, $-C(O)NR^{11}R^{12}$, $-C(O)NR^{11}OH$, $-S(O)_2R^{11}$, $-S(O)R^{11}$, $-S(O)_2NR^{11}R^{12}$, $-NR^{11}S(O)_2R^{11}$, $-P(O)(OR^{11})_2$, y $-OP(O)(OR^{11})_2$;

cada R^9 se selecciona, de manera independiente, de H, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-S(O)_2R^{10}$, alquilo C_1–C_6, heteroalquilo C_1–C_6 y cicloalquilo C_3–C_6; o cada R^9 es, de modo independiente, un alquilo C_1–C_6 que, junto con N, están unidos para formar un heterocicloalquilo C_3–C_8, donde el anillo heterocicloalquilo C_3–C_8 opcionalmente contiene un heteroátomo adicional seleccionado de N, O y S, y donde los grupos alquilo C_1–C_6, heteroalquilo C_1–C_6, cicloalquilo C_3–C_6, o heterocicloalquilo C_3–C_8 de R^9 están, cada uno, opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente de –CN, R^{11}, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-OC(O)R^{11}$,

$-C(O)OR^{11}$, $-NR^{11}R^{12}$, $-C(O)NR^{11}R^{12}$, $-C(O)NR^{11}OH$, $-S(O)_2R^{11}$, $-S(O)R^{11}$, $-S(O)_2NR^{11}R^{12}$, $-NR^{11}S(O)_2R^{11}$, $-P(O)(OR^{11})_2$, y $-OP(O)(OR^{11})_2$;

cada R^{10} se selecciona, de manera independiente, de arilo, cicloalquilo C_3–C_8, heterocicloalquilo C_3–C_8 o un heteroarilo, donde los grupos arilo, cicloalquilo C_3–C_8, heterocicloalquilo C_3–C_8 o heteroarilo están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de halógeno, $-R^8$, $-OR^8$, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9CO_2R^8$, $-CO_2R^8$, $-C(O)R^8$ y $-C(O)N(R^9)_2$;

R^{11} y R^{12} se seleccionan de manera independiente de H, alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8, donde los grupos alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8 de R^{11} y R^{12}, de manera independiente, están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de modo independiente de halógeno, –CN, R^8, $-OR^8$, $-C(O)R^8$, $^-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-NR^8C(O)R^8$, $-NR^8C(O)OR^8$, $-C(O)N(R^9)_2$, heterocicloalquilo C_3–C_8, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, $-NR^9S(O)_2R^8$, haloalquilo C_1–C_6 y haloalcoxi C_1–C_6, y donde los grupos arilo y heteoarilo de R^{11} y R^{12} están, cada uno, opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente de halógeno, –CN, R^8, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-C(O)N(R^9)_2$, heterocicloalquilo C_3–C_8, $-S(O)_2R^8$, $-S(O)_2\ N(R^9)_2$, $-NR^9S(O)_2R^8$, haloalquilo C_1–C_6 y haloalcoxi C_1–C_6; o R^{11} y R^{12} son, cada uno de modo independiente, alquilo C_1–C_6, y tomados junto con el átomo de N al cual están unidos forman un heterocicloalquilo C_3–C_8 opcionalmente sustituido. que contiene opcionalmente un heteroátomo adicional seleccionado de N, O y S;

el anillo A es un arilo o un heteroarilo, donde los grupos arilo y heteroarilo del Anillo A están opcionalmente sustituidos con 1 a 3 grupos R^A, donde cada R^A se selecciona de manera independiente de $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$,

$-SR^8$, $-NO_2$, $-CN$, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$ y $-(CH_2)_nNHC(O)R^8$; o dos sustituyentes R^A adyacentes en el anillo A forman un anillo de 5–6 miembros que contiene hasta dos heteroátomos como miembros de anillo; y n es, de manera independiente en cada aparición, 0, 1; 2; 3; 4; 5; 6; 7 u 8; cada m se selecciona de manera independiente de 1, 2, 3, 4, 5 y 6, y t es 1, 2, 3, 4, 5, 6, 7 u 8.

En ciertas realizaciones de dichos compuestos de Fórmulas (I) o (I-A), uno de R^4 y R^5 es H; y el otro de R^4 y R^5 se selecciona de halógeno, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, $-SR^7$, $-(CH_2)_nOR^7$, $-(CH_2)_nR^7$, alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8, y heterocicloalquilo C_3–C_8, donde los grupos alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8, y heterocicloalquilo C_3–C_8 de R^4 y R^5 están, cada uno, opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente de halógeno, –CN, $-R^7$, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-C(O)N(R^9)_2$, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, y $-NR^9S(O)_2R^8$.

En ciertas realizaciones de dichos compuestos de Fórmulas (I) o (I-A), el anillo A es fenilo, naftilo, fluorenilo, indenilo, azulenilo o antracenilo, cada uno de

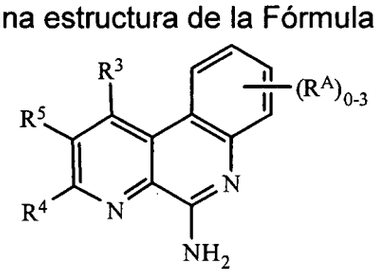
los cuales está opcionalmente sustituido con 1 a 3 grupos R^A, donde cada R^A se selecciona de manera independiente de $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, $-CN$, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$, y $-(CH_2)_nNHC(O)R^8$. En ciertas realizaciones de dichos compuestos de Fórmulas (I) o (I-A), el anillo A es fenilo o naftilo.

En ciertas realizaciones de dichos compuestos de las Fórmulas (I) o (I–A), el anillo A es fenilo, naftilo, fluorenilo, indenilo, azulenilo o antracenilo, cada uno de los cuales está opcionalmente sustituido con 1 a 3 grupos R^A, donde cada R^A se selecciona de modo independiente de $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, $-CN$, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$ y $-(CH_2)_nNHC(O)R^8$. En ciertas realizaciones de dichos compuestos de las Fórmulas (I) o (I–A), el anillo A es fenilo o naftilo.

En ciertas realizaciones de dichos compuestos de las Fórmulas (I) o (I–A), el anillo A es benzofuranilo, benzofurazanilo, benzoxazolilo, benzopiranilo, benztiazolilo, benzotienilo, benzazepinilo, bencimidazolilo, benzotiopiranilo,

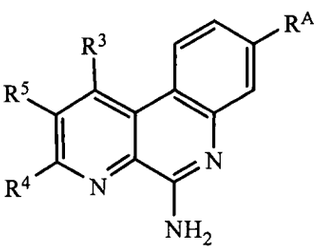
benzo[1,3]dioxol, benzo[b]furilo, benzo[b]tienilo, cinolinilo, furazanilo, furilo, furopiridinilo, imidazolilo, indolilo, indolizinilo, indolin–2–ona, indazolilo, isoindolilo, isoquinolinilo, isoxazolilo, isotiazolilo, 1,8–naftiridinilo, oxazolilo, oxaindolilo, oxadiazolilo, pirazolilo, pirrolilo, ftalazinilo, pteridinilo, purinilo, piridilo, piridazinilo, pirazinilo, pirimidinilo, quinoxalinilo, quinolinilo, quinazolinilo, 4H–quinolizinilo, tiazolilo, tiadiazolilo, tienilo, triazinilo, triazolilo o tetrazolilo, cada uno de los cuales está opcionalmente sustituido con 1 a 3 grupos R^A, donde cada R^A se selecciona de modo independiente de $–R^8$, $–R^7$, $–OR^7$, $–OR^8$, $–R^{10}$, $–OR^{10}$, $–SR^8$, $–NO_2$, $–CN$, $–N(R^9)_2$, $–NR^9C(O)R^8$, $–NR^9C(S)R^8$, $–NR^9C(O)N(R^9)_2$, $–NR^9C(S)N(R^9)_2$, $–NR^9CO_2R^8$, $–NR^9NR^9C(O)R^8$, $–NR^9NR^9C(O)N(R^9)_2$, $–NR^9NR^9CO_2R^8$, $–C(O)C(O)R^8$, $–C(O)CH_2C(O)R^8$, $–CO_2R^8$, $–(CH_2)_nCO_2R^8$, $–C(O)R^8$, $–C(S)R^8$, $–C(O)N(R^9)_2$, $–C(S)N(R^9)_2$, $–OC(O)N(R^9)_2$, $–OC(O)R^8$, $–C(O)N(OR^8)R^8$, $–C(NOR^8)R^8$, $–S(O)_2R^8$, $–S(O)_3R^8$, $–SO_2N(R^9)_2$, $–S(O)R^8$, $–NR^9SO_2N(R^9)_2$, $–NR^9SO_2R^8$, $–P(O)(OR^8)_2$, $–OP(O)(OR^8)_2$, $–P(O)(OR^{10})_2$, $–OP(O)(OR^{10})_2$, $–N(OR^8)R^8$, $–CH=CHCO_2R^8$, $–C(=NH)–N(R^9)_2$ y $–(CH_2)_nNHC(O)R^8$. En ciertas realizaciones de dichos compuestos de las Fórmulas (I) o (I–A), el anillo A es piridilo, benzo[1,3]dioxol, tienilo, benzotienilo, benzofuranilo o indolilo.

En ciertas realizaciones de los compuestos de la Fórmula (I) y la Fórmula (I–A), los compuestos tienen una estructura de la Fórmula (X):



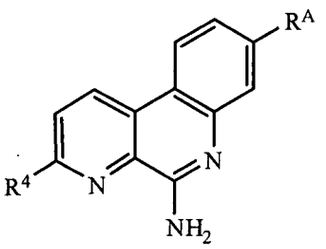
Fórmula (X-A).

En ciertas realizaciones de los compuestos de la Fórmula (I) o la Fórmula (I–A), los compuestos tienen una estructura de la Fórmula (XI):

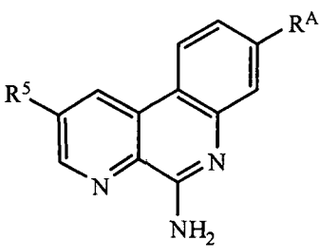


Fórmula (XI).

En ciertas realizaciones de los compuestos de la Fórmula (I) o la Fórmula (I–A), los compuestos tienen una estructura de la Fórmula (XII) o la Fórmula (XIII):



Fórmula (XII)

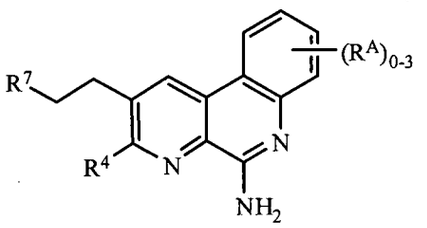


Fórmula (XIII).

En ciertas realizaciones de dichos compuestos de las Fórmulas (I) o (I–A), Fórmulas (X-A) y (XI) a (XIII), R^4 y R^5 se seleccionan de manera independiente de H, halógeno, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, $-SR^7$, $-(CH_2)_nR^7$, $-(CH_2)_nOR^7$, –alquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8 y alcoxi C_1–C_6, donde los grupos alquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8 y alcoxi C_1–C_6 de R^4 y R^5, de manera independiente, están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de modo independiente de halógeno, –CN, $-R^7$, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-C(O)N(R^9)_2$, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, y $-NHS(O)_2R^8$. En otras realizaciones de dichos compuestos de las Fórmulas (I) o (I–A), Fórmulas (X-A) y (XI) a (XIII), R^4 y R^5 se seleccionan de manera independiente de H, halógeno, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, $-SR^7$, $-(CH_2)_nOR^7$, $-(CH_2)_nR^7$, –alquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8 y alcoxi C_1–C_6, donde los grupos alquilo $-C_1$–C_6, haloalquilo C_1–C_6,

alqueno C_2–C_8, alquino C_2–C_8 y alcoxi C_1–C_6, de manera independiente, están opcionalmente sustituidos con R^7.

En ciertas realizaciones de los compuestos de la Fórmula (I) y la Fórmula (I–A), los compuestos tienen una estructura de la Fórmula (XIV):



Fórmula (XIV).

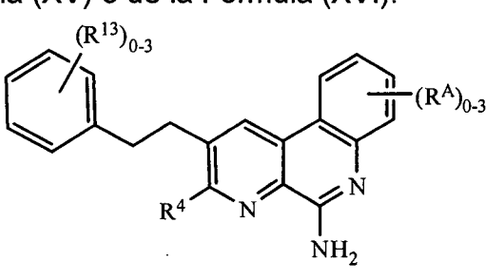
En ciertas realizaciones de dichos compuestos de la Fórmula (XIV), R^4 se selecciona de H, halógeno, –C(O)OR^7, –C(O)R^7, –C(O)N($R^{11}R^{12}$), –N($R^{11}R^{12}$), –SR^7, –$(CH_2)_nR^7$, –$(CH_2)_nOR^7$, –alquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8 y alcoxi C_1–C_6, donde los grupos alquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8 y alcoxi C_1–C_6 de R^4 y R^5, de manera independiente, están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de modo independiente de halógeno, –CN, –R^7, –OR^8, –C(O)R^8, –OC(O)R^8, –C(O)OR^8, –N(R^9)$_2$, –P(O)(OR^8)$_2$, –OP(O)(OR^8)$_2$, –P(O)(OR^{10})$_2$, –OP(O)(OR^{10})$_2$, –C(O)N(R^9)$_2$, –S(O)$_2R^8$, –S(O)$_2$ N(R^9)$_2$ y –NHS(O)$_2R^8$. En otras realizaciones de dichos compuestos de la Fórmula (XIV), R^4 se selecciona de H, halógeno, –C(O)OR^7, –C(O)R^7, –C(O)N($R^{11}R^{12}$), –N($R^{11}R^{12}$), –SR^7, –$(CH_2)_nOR^7$, –$(CH_2)_nR^7$, –alquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8 y alcoxi C_1–C_6, donde los grupos –alquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8 y alcoxi C_1–C_6, de modo independiente, están opcionalmente sustituidos con R^7.

En ciertas realizaciones de dichos compuestos de las Fórmulas (I) o (I–A), Fórmulas (X-A) y (XI) a (XIV), R^7 se selecciona de H, alquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8, donde los grupos alquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8 de R^7, de

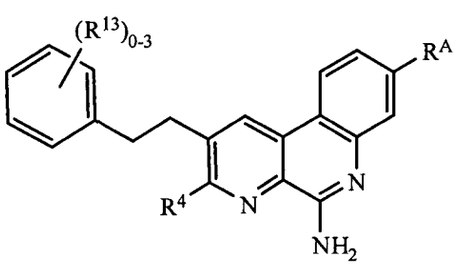
modo independiente, están opcionalmente sustituidos con 1 a 3 grupos R^{13}, y donde cada R^{13} se selecciona de manera independiente de halógeno, –CN, $–LR^9$, $–LOR^9$, $–OLR^9$, $–LR^{10}$, $–LOR^{10}$, $–OLR^{10}$, $–LR^8$, $–LOR^8$, $–OLR^8$, $–LSR^8$, $–LSR^{10}$, $–LC(O)R^8$, $–OLC(O)R^8$, $–LC(O)OR^8$, $–LC(O)R^{10}$, $–LOC(O)OR^8$, $–LC(O)NR^9R^{11}$, $–LC(O)NR^9R^8$, $–LN(R^9)_2$, $–LNR^9R^8$, $–LNR^9R^{10}$, $–LC(O)N(R^9)_2$, $–LS(O)_2R^8$, $–LS(O)R^8$, $–LC(O)NR^8OH$, $–LNR^9C(O)R^8$, $–LNR^9C(O)OR^8$, $–LS(O)_2N(R^9)_2$, $–OLS(O)_2N(R^9)_2$, $–LNR^9S(O)_2R^8$, $–LC(O)NR^9LN(R^9)_2$, $–LP(O)(OR^8)_2$, $–LOP(O)(OR^8)_2$, $–LP(O)(OR^{10})_2$ y $–OLP(O)(OR^{10})_2$.

En ciertas realizaciones de dichos compuestos de las Fórmulas (I) o (I–A), Fórmulas (X-A) y (XI) a (XIV), R^7 se selecciona de H, alquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8, donde los grupos alquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8 de manera independiente están opcionalmente sustituidos con 1–3 grupos R^{13}, y donde cada R^{13} se selecciona de modo independiente de halógeno, haloalquilo C_1–C_6, LR^8, LR^9, $–LOR^8$ y $–OLR^8$.

En ciertas realizaciones de los compuestos de las Fórmulas (I) o (I–A), Fórmulas (X-A) y (XI) a (XIV), los compuestos tienen una estructura de la Fórmula (XV) o de la Fórmula (XVI):



Fórmula (XV)



Fórmula (XVI).

En ciertas realizaciones de dichos compuestos de las Fórmulas (I) o (I–A), Fórmulas (X-A) y (XI) a (XVI), R^{13} se selecciona de $–LR^9$, $–LOR^9$, $–OLR^9$, $–LR^{10}$, $–LOR^{10}$, $–OLR^{10}$, $–LR^8$, $–LOR^8$, $–OLR^8$, $–LSR^8$, $–LSR^{10}$, $–LC(O)R^8$, $–OLC(O)R^8$, $–LC(O)OR^8$, $–LC(O)R^{10}$, $–LOC(O)OR^8$,

$-LC(O)NR^9R^{11}$, $-LC(O)NR^9R^8$, $-LN(R^9)_2$, $-LNR^9R^8$, $-LNR^9R^{10}$, $-LC(O)N(R^9)_2$, $-LS(O)_2R^8$, $-LS(O)R^8$, $-LC(O)NR^8OH$, $-LNR^9C(O)R^8$, $-LNR^9C(O)OR^8$, $-LS(O)_2N(R^9)_2$, $-OLS(O)_2N(R^9)_2$, $-LNR^9S(O)_2R^8$, $-LC(O)NR^9LN(R^9)_2$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$ y $-OLP(O)(OR^{10})_2$.

En ciertas realizaciones de dichos compuestos de las Fórmulas (I) o (I–A), Fórmulas (X-A) y (XI) a (XVI), R^{10} es un arilo o heteroarilo, donde los grupos arilo y heteroarilo están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de halógeno, $-R^8$, $-OR^8$ y $-N(R^9)_2$.

En ciertas realizaciones de dichos compuestos de las Fórmulas (I) o (I–A), Fórmulas (X-A) y (XI) a (XVI), R^{10} es fenilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de halógeno, $-R^8$, $-OR^8$ y $-N(R^9)_2$.

En ciertas realizaciones de dichos compuestos de las Fórmulas (I) o (I–A), Fórmulas (X-A) y (XI) a (XVI), R^8 se selecciona de H, alquilo C_1–C_6 y haloalquilo C_1–C_6. En ciertas realizaciones de los compuestos de las Fórmulas XIII, XIV, XV o XVI, el compuesto se selecciona de: 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol; 2–(4–metoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato; 2–(4–(dimetilamino)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina y 2–(4–metoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina. Cada uno de estos compuestos representa individualmente una realización preferida de los compuestos, las composiciones y los métodos que se describen en la presente solicitud.

En ciertas realizaciones preferidas de los compuestos, las composiciones y los métodos que se describen en la presente solicitud, el compuesto de la

Fórmula (I) se selecciona de:

2–metilbenzo[f][1,7]naftiridin–5–amina; 2–propilbenzo[f][1,7]naftiridin–5–amina; 2–etilbenzo[f][1,7]naftiridin–5–amina; 2–(3–(trifluorometil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,4–difluorfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(3–metoxifenetil)benzo[f][1,7]naftiridin–5–amina; 8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–fenetilbenzo[f][1,7]naftiridin–5–amina; metil 5–aminobenzo[f][1,7]naftiridina–3–carboxilato; 5–amino–N–metilbenzo[f][1,7]naftiridina–3–carboxamida; (5–aminobenzo[f][1,7]naftiridin–3–il)metanol; 8–fenilbenzo[f][1,7]naftiridin–5–amina; 3–(etoximetil)benzo[f][1,7]naftiridin–5–amina; benzo[f][1,7]naftiridina–3,5–diamina; benzo[f][1,7]naftiridin–5–amina; metil 5–aminobenzo[f][1,7]naftiridina–8–carboxilato; ácido 5–aminobenzo[f][1,7]naftiridina–8–carboxílico; etil 5–aminobenzo[f][1,7]naftiridina–8–carboxilato; (5–aminobenzo[f][1,7]naftiridin–8–il)metanol; ácido 5–aminobenzo[f][1,7]naftiridina–3–carboxílico; 5–aminobenzo[f][1,7]naftiridina–3–carbaldehído; 2–(2–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(3–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 8–clorobenzo[f][1,7]naftiridin–5–amina; etil 5–aminobenzo[f][1,7]naftiridina–9–carboxilato; 8–metoxibenzo[f][1,7]naftiridin–5–amina; 8–(metilsulfonil)benzo[f][1,7]naftiridin–5–amina; 8–(trifluorometil)benzo[f][1,7]naftiridin–5–amina; 8–fluorbenzo[f][1,7]naftiridin–5–amina; 3–metoxibenzo[f][1,7]naftiridin–5–amina; 3–butoxibenzo[f][1,7]naftiridin–5–amina; 3–(benciloxi)benzo[f][1,7]naftiridin–5–amina; 3–metilbenzo[f][1,7]naftiridin–5–amina; 3–clorobenzo[f][1,7]naftiridin–5–amina; N3,N3–dimetilbenzo[f][1,7]naftiridina–3,5–diamina; N3–butilbenzo[f][1,7]naftiridina–3,5–diamina; 3–vinilbenzo[f][1,7]naftiridin–5–amina; 3–etilbenzo[f][1,7]naftiridin–5–

amina; 3–fluorbenzo[f][1,7]naftiridin–5–amina; 2–fenetilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2–(naftalen–1–il)etil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2–(naftalen–2–il)etil)benzo[f][1,7]naftiridin–5–amina; ácido 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoico; ácido 3–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoico; 2–(3–clorofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–clorofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; (3–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)metanol; 2–(4–clorofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–butilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–butilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–propilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(trifluormetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,5–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–propilfenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2,4,5–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,5–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–isopropilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–heptilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–isobutoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–((2–metoxietoxi)metoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(2–fenoxietoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(ter–butildimetilsililoxi)etoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(4–fenilbutoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(aliloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(3–fenilpropoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(heptan–4–iloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(4–metilpent–3–eniloxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–ciclohexiletoxi)fenetil)–8–

metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–isopropoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(3,3–dimetilbutoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(ter–butildimetilsililoxi)etoxi)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)–2–(4–(dimetilamino)fenetil)benzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)–2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; N–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)acetamida; N–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)fenil)acetamida; N–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)–4–metilbencenosulfonamida; 3–metil–9–p–tolil–9,10–dihidrobenzo[f]furo[2,3–b][1,7]naftiridin–6–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzonitrilo; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–aminoetil)–3–metilbenzamida; 8–metil–2–(2–metil–4–(1H–tetrazol–5–il)fenetil)benzo[f][1,7]naftiridin–5–amina; metil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)–4–metilpentanoato; metil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)acetato; ácido 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)–4–metilpentanoico; ácido 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)acético; 6–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)hexan–1–ol; ácido 7–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)heptanoico; 11–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)undecan–1–ol; etil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)acetato; ácido 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)acético; ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propanoico; ácido 6–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)hexanoico; 8–metil–2–(2–metil–4–(metiltio)fenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–

(metilsulfonil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(hexiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–fenetoxifenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(pentiloxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(4–metilpentiloxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2–fluorfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(3–fluorfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–fluorfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2–(tiofen–3–il)etil)benzo[f][1,7]naftiridin–5–amina; (5–aminobenzo[f][1,7]naftiridin–2–il)metanol; 2–(3,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(3,4–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(3,5–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(benzofuran–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2–nitroetil)benzo[f][1,7]naftiridin–5–amina; 2–(aminometil)–8–metilbenzo[f][1,7]naftiridin–5–amina; N2,8–dimetilbenzo[f][1,7]naftiridina–2,5–diamina; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–feniletanol; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–(4–metoxifenil)etanol; 2–(bifenil–2–il)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(2,6–dimetilpiridin–3–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(5–metoxipiridin–2–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propanoico; 5–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–4–metilpiridin–2(1H)–ona; 6–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)piridin–3–ol; 8–metil–2–(4–(trifluormetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2–(2,3–dihidro–1H–inden–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(2,3–dihidro–1H–inden–5–il)etil)benzo[f][1,7]naftiridin–5–amina; ácido (E)–3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)acrílico; (E)–etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)acrilato; 8–(prop–1–en–2–

il)benzo[f][1,7]naftiridin–5–amina; 5–aminobenzo[f][1,7]naftiridina–8–carbonitrilo; (E)–8–(3–metilbut–1–enil)benzo[f][1,7]naftiridin–5–amina; 8–(2–metilprop–1–enil)benzo[f][1,7]naftiridin–5–amina; (E)–8–(pent–1–enil)benzo[f][1,7]naftiridin–5–amina; (E)–8–estirilbenzo[f][1,7]naftiridin–5–amina; (E)–8–(2–ciclopropilvinil)–2–fenetilbenzo[f][1,7]naftiridin–5–amina; 8–pentilbenzo[f][1,7]naftiridin–5–amina; (E)–8–(2–ciclopropilvinil)benzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)–2–fenetilbenzo[f][1,7]naftiridin–5–amina; 9–fenetilpirido[1,2–c][1,7]naftiridin–6–amina; metil 5–amino–2–(4–metoxifenetil)benzo[f][1,7]naftiridina–8–carboxilato; 8–nitrobenzo[f][1,7]naftiridin–5–amina; 3–cloro–8–metilbenzo[f][1,7]naftiridin–5–amina; metil 5–amino–3–clorobenzo[f][1,7]naftiridina–8–carboxilato; metil 5–amino–3–fluorbenzo[f][1,7]naftiridina–8–carboxilato; 3–cloro–8–nitrobenzo[f][1,7]naftiridin–5–amina; (5–amino–3–clorobenzo[f][1,7]naftiridin–8–il)metanol; (5–amino–2–fenetilbenzo[f][1,7]naftiridin–8–il)metanol; 4–(2–(5–amino–8–fluorbenzo[f][1,7]naftiridin–2–il)etil)benzaldehído; 2–(4–(2–(5–amino–8–fluorbenzo[f][1,7]naftiridin–2–il)etil)bencilamino)etanol; 3–(4–(2–(5–amino–8–fluorbenzo[f][1,7]naftiridin–2–il)etil)bencilamino)propan–1–ol; 8–fluor–2–(4–((2–metoxietilamino)metil)fenetil)benzo[f][1,7]naftiridin–5–amina; (5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)metanol; 3–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)fenol; 2–(2–metoxifenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–etilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–etilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(dimetilamino)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(piperidin–1–il)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–ter–butilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(piperidin–1–il)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–metoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(3,5–dimetoxifenetil)–8–

metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2–(trifluormetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–hidroxibencimidamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzonitrilo; 8–metil–2–(4–(1–morfolinoetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–aminofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)guanidina; 8–metil–2–(4–(1–(fenetilamino)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)acetonitrilo; 2–(4–(piperidin–1–ilmetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 1–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)bencil)piperidin–4–ol; 2–(4–(aminometil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–((etilamino)metil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–aminopropan–2–il)fenetil)benzo[f][1,7]naftiridin–5–amina; ácido 1–(1–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidina–3–carboxílico; 8–metil–2–(4–(1–(fenilamino)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–etil–8–metilbenzo[f][1,7]naftiridin–5–amina; (5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)metanol; 8–metil–2–propilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(1H–indol–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–etoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–fenoxifenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,4–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–metoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol; 2–(2–(2,3–dihidrobenzofuran–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etanol; 3–metil–9–fenil–9,10–

dihidrobenzo[f]furo[2,3–b][1,7]naftiridin–6–amina; 8–metilbenzo[f][1,7]naftiridina–2,5–diamina; 1–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)propan–2–ol; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)acetonitrilo; N–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)acetamida; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–(2,4–dimetilfenil)etanol; 2–(2–(6–metoxi–4–metilpiridin–3–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)butan–1–ol; metil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propanoato; 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propan–1–ol; 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)–2–metilbutan–2–ol; 2–(4–(aminometil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; (E)–etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)acrilato; etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propanoato; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbencil)propano–1,3–diol; ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propanoico; 5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridina–8–carbaldehído; etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoato; 8–metil–2–(4–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propan–2–ol; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)metanol; etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato; ácido 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoico; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)metanol; 8–metil–2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol; 8–metil–2–(4–propoxifenetil)benzo[f][1,7]naftiridin–5–amina; ácido (E)–3–(5–amino–2–(4–

metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)acrílico; etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propanoato; ácido 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propanoico; 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propan–1–ol; 5–aminobenzo[f][1,7]naftiridin–8–ol; 5–aminobenzo[f][1,7]naftiridina–8–carbaldehído; 1–(5–aminobenzo[f][1,7]naftiridin–8–il)etanol; 1–(5–aminobenzo[f][1,7]naftiridin–8–il)etanona; 8–isopropilbenzo[f][1,7]naftiridin–5–amina; 8–vinilbenzo[f][1,7]naftiridin–5–amina; 8–etilbenzo[f][1,7]naftiridin–5–amina; 8–(metoximetil)benzo[f][1,7]naftiridin–5–amina; (5–amino–2–(4–metoxifenetil)benzo[f][1,7]naftiridin–8–il)metanol; benzo[f][1,7]naftiridina–5,8–diamina; 8–(aminometil)benzo[f][1,7]naftiridin–5–amina; 3–fluor–8–metilbenzo[f][1,7]naftiridin–5–amina; (5–amino–3–fluorbenzo[f][1,7]naftiridin–8–il)metanol; 3–clorobenzo[f][1,7]naftiridina–5,8–diamina; 3–fluorbenzo[f][1,7]naftiridina–5,8–diamina; 8–isobutilbenzo[f][1,7]naftiridin–5–amina; (E)–8–(prop–1–enil)benzo[f][1,7]naftiridin–5–amina; 8–propilbenzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)benzo[f][1,7]naftiridin–5–amina; 8–fenetilbenzo[f][1,7]naftiridin–5–amina; (5–amino–2–(4–bromofenetil)benzo[f][1,7]naftiridin–8–il)metanol; (5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)metanol; 2–(4–metoxi–2–metilfenetil)–8–pentilbenzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–5–amina; (5–amino–2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–8–il)metanol; (5–amino–2–(4–propoxifenetil)benzo[f][1,7]naftiridin–8–il)metanol; (2–(2–(1H–indol–5–il)etil)–5–aminobenzo[f][1,7]naftiridin–8–il)metanol; metil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N,3–dimetilbenzamida; N–(2–acetamidoetil)–4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamida; 4–(2–

(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N,3–dimetilbenzamida; 2–(4–metoxifenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N,N,3–trimetilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–hidroxietil)–3–metilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–3–metilbenzamida; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(pirrolidin–1–il)metanona; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dietilamino)etil)–3–metilbenzamida; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(4–etilpiperazin–1–il)metanona; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(piperazin–1–il)metanona; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metil–N–(2–(pirrolidin–1–il)etil)benzamida; 4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N,3–dimetilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N–metilbenzamida; 2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol; 2–(4–butoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(bifenil–4–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–((1,3–dihidroisobenzofuran–1–il)metil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(2–metilaliloxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(isopentiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil propil carbonato; etil 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)pentanoato; 2–(4–(ciclopentiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(ciclobutilmetoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(2–morfolinoetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–amino–8–

metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)–1–feniletanona; ácido 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)pentanoico; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)etanol; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)–N,N–dimetilacetamida; 8–metil–2–(2–metil–4–(2–morfolinoetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etanol; dietil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propilfosfonato; ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propilfosfónico; 2–(4–butoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol; 2–(2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etanol; etil 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)pentanoato; ácido 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)pentanoico; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil etil carbonato; metil 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)butanoato; ácido 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)butanoico; ácido 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)butanoico; 2–(4–(isopentiloxi)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil hexil carbonato; 2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina; (5–amino–2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–8–il)metanol; dietil 3–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)propilfosfonato; dietil 3–(2–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etoxi)propilfosfonato; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil dimetilsulfamato; (5–amino–2–(4–

(dimetilamino)fenetil)benzo[f][1,7]naftiridin–8–il)metanol; 2–(4–(dimetilamino)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol; 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona; 2–(4–((dimetilamino)metil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(1–(dimetilamino)etil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona oxima; 8–metil–2–(4–((metilamino)metil)fenetil)benzo[f][1,7]naftiridin–5–amina; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)bencilamino)etanol; 8–metil–2–(4–(pirrolidin–1–ilmetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(3,4–dimetoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)etanol; 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanol; 8–metil–2–(4–(oxazol–5–il)fenetil)benzo[f][1,7]naftiridin–5–amina; 3–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propanonitrilo; (2R)–2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propan–1–ol; 8–metil–2–(4–(1–(piperazin–1–il)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; ((2S)–1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidin–2–il)metanol; N1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N2,N2–dimetiletano–1,2–diamina; ácido 3–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propanoico; 8–metil–2–(4–(1–(4–metilpiperazin–1–il)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; N2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N1,N1–dimetilpropano–1,2–diamina; 8–metil–2–(4–(1–(2–(piridin–4–il)etilamino)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; N1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N2,N2–dietiletano–1,2–diamina; 2–(4–(dimetilamino)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; ácido 1–

(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidina–3–carboxílico; 4–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)fenol; 1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2 il)etil)fenil)etil)pirrolidin–3–ol y 2–(4–(2–aminopropan–2–il)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

En ciertas realizaciones de los compuestos, las composiciones y los métodos que se describen en la presente solicitud, el compuesto de la Fórmula (I–A) se selecciona de los siguientes compuestos y sus sales aceptables para uso farmacéutico:

2–metilbenzo[f][1,7]naftiridin–5–amina; 2–propilbenzo[f][1,7]naftiridin–5–amina; 2–etilbenzo[f][1,7]naftiridin–5–amina; 2–(3–metoxifenetil)benzo[f][1,7]naftiridin–5–amina; 8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–fenetilbenzo[f][1,7]naftiridin–5–amina; metil 5–aminobenzo[f][1,7]naftiridina–3–carboxilato; (5–aminobenzo[f][1,7]naftiridin–3–il)metanol; benzo[f][1,7]naftiridin–5–amina; (5–aminobenzo[f][1,7]naftiridin–8–il)metanol; 2–(2–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(3–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 8–clorobenzo[f][1,7]naftiridin–5–amina; etil 5–aminobenzo[f][1,7]naftiridina–9–carboxilato; 8–metoxibenzo[f][1,7]naftiridin–5–amina; 8–(trifluormetil)benzo[f][1,7]naftiridin–5–amina; 8–fluorbenzo[f][1,7]naftiridin–5–amina; 3–metilbenzo[f][1,7]naftiridin–5–amina; 3–fluorbenzo[f][1,7]naftiridin–5–amina; 2–fenetilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2–(naftalen–1–il)etil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2–(naftalen–2–il)etil)benzo[f][1,7]naftiridin–5–amina; ácido 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoico; ácido 3–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoico; 2–(3–clorofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–clorofenetil)–8–

metilbenzo[f][1,7]naftiridin–5–amina; (3–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)metanol; 2–(4–clorofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–butilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–butilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–propilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(trifluormetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,5–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–propilfenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2,4,5–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,5–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–isopropilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–heptilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–isobutoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–((2–metoxietoxi)metoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(2–fenoxietoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(4–fenilbutoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(aliloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(3–fenilpropoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(heptan–4–iloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(4–metilpent–3–eniloxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–ciclohexiletoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–isopropoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(3,3–dimetilbutoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)–2–(4–(dimetilamino)fenetil)benzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)–2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; N–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)acetamida; N–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)fenil)acetamida; N–(4–(2–(5–amino–8–

metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)–4–metilbencenosulfonamida; 3–metil–9–p–tolil–9,10–dihidrobenzo[f]furo[2,3–b][1,7]naftiridin–6–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzonitrilo; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–aminoetil)–3–metilbenzamida; 8–metil–2–(2–metil–4–(1H–tetrazol–5–il)fenetil)benzo[f][1,7]naftiridin–5–amina; metil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)–4–metilpentanoato; metil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)acetato; ácido 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)–4–metilpentanoico; ácido 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)acético; 6–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)hexan–1–ol; ácido 7–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)heptanoico; 11–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)undecan–1–ol; etil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)acetato; ácido 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)acético; ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propanoico; ácido 6–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)hexanoico; 8–metil–2–(2–metil–4–(metiltio)fenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(metilsulfonil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(hexiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–fenetoxifenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(pentiloxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(4–metilpentiloxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2–fluorfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(3–fluorfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–fluorfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2–(tiofen–3–il)etil)benzo[f][1,7]naftiridin–5–amina; (5–aminobenzo[f][1,7]naftiridin–2–il)metanol;

2–(3,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(3,4–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(3,5–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(benzofuran–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2–nitroetil)benzo[f][1,7]naftiridin–5–amina; 2–(aminometil)–8–metilbenzo[f][1,7]naftiridin–5–amina; N^2,8–dimetilbenzo[f][1,7]naftiridina–2,5–diamina; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–feniletanol; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–(4–metoxifenil)etanol; 2–(bifenil–2–il)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(2,6–dimetilpiridin–3–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(5–metoxipiridin–2–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propanoico; 5–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–4–metilpiridin–2(1H)–ona; 6–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)piridin–3–ol; 8–metil–2–(4–(trifluormetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2–(2,3–dihidro–1H–inden–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(2,3–dihidro–1H–inden–5–il)etil)benzo[f][1,7]naftiridin–5–amina; ácido (E)–3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)acrílico; (E)–etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)acrilato; (E)–8–(2–ciclopropilvinil)–2–fenetilbenzo[f][1,7]naftiridin–5–amina; 8–pentilbenzo[f][1,7]naftiridin–5–amina; (E)–8–(2–ciclopropilvinil)benzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)–2–fenetilbenzo[f][1,7]naftiridin–5–amina; (5–amino–2–fenetilbenzo[f][1,7]naftiridin–8–il)metanol; (5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)metanol; 3–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)fenol; 2–(2–metoxifenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–etilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–etilfenetil)–8–

metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(dimetilamino)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(piperidin–1–il)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–ter–butilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(piperidin–1–il)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–metoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(3,5–dimetoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2–(trifluormetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–hidroxibencimidamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzonitrilo; 8–metil–2–(4–(1–morfolinoetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–aminofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)guanidina; 8–metil–2–(4–(1–(fenetilamino)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)acetonitrilo; 2–(4–(piperidin–1–ilmetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 1–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)bencil)piperidin–4–ol; 2–(4–(aminometil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–((etilamino)metil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–aminopropan–2–il)fenetil)benzo[f][1,7]naftiridin–5–amina; ácido 1–(1–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidina–3–carboxílico; 8–metil–2–(4–(1–(fenilamino)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–etil–8–metilbenzo[f][1,7]naftiridin–5–amina; (5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)metanol; 8–metil–2–propilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(1H–indol–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–etoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–fenoxifenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,4–

dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,4–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–metoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol; 2–(2–(2,3–dihidrobenzofuran–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etanol; 3–metil–9–fenil–9,10–dihidrobenzo[f]furo[2,3–b][1,7]naftiridin–6–amina; 8–metilbenzo[f][1,7]naftiridina–2,5–diamina; 1–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)propan–2–ol; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)acetonitrilo; N–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)acetamida; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–(2,4–dimetilfenil)etanol; 2–(2–(6–metoxi–4–metilpiridin–3–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)butan–1–ol; metil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propanoato; 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propan–1–ol; 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)–2–metilbutan–2–ol; 2–(4–(aminometil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; (E)–etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)acrilato; etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propanoato; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbencil)propano–1,3–diol; ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propanoico; 5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridina–8–carbaldehído; etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoato; 8–metil–2–(4–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propan–2–ol; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)metanol; etil 4–(2–(5–amino–8–

metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato; ácido 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoico; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)metanol; 8–metil–2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol; 8–metil–2–(4–propoxifenetil)benzo[f][1,7]naftiridin–5–amina; ácido (E)–3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)acrílico; etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propanoato; ácido 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propanoico; 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propan–1–ol; 5–aminobenzo[f][1,7]naftiridin–8–ol; 5–aminobenzo[f][1,7]naftiridina–8–carbaldehído; 1–(5–aminobenzo[f][1,7]naftiridin–8–il)etanol; 1–(5–aminobenzo[f][1,7]naftiridin–8–il)etanona; 8–isopropilbenzo[f][1,7]naftiridin–5–amina; 8–vinilbenzo[f][1,7]naftiridin–5–amina; 8–etilbenzo[f][1,7]naftiridin–5–amina; 8–(metoximetil)benzo[f][1,7]naftiridin–5–amina; (5–amino–2–(4–metoxifenetil)benzo[f][1,7]naftiridin–8–il)metanol; benzo[f][1,7]naftiridina–5,8–diamina; 8–(aminometil)benzo[f][1,7]naftiridin–5–amina; 3–fluor–8–metilbenzo[f][1,7]naftiridin–5–amina; (5–amino–3–fluorbenzo[f][1,7]naftiridin–8–il)metanol; 3–clorobenzo[f][1,7]naftiridina–5,8–diamina; 3–fluorbenzo[f][1,7]naftiridina–5,8–diamina; 8–isobutilbenzo[f][1,7]naftiridin–5–amina; (E)–8–(prop–1–enil)benzo[f][1,7]naftiridin–5–amina; 8–propilbenzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)benzo[f][1,7]naftiridin–5–amina; 8–fenetilbenzo[f][1,7]naftiridin–5–amina; (5–amino–2–(4–bromofenetil)benzo[f][1,7]naftiridin–8–il)metanol; 2–(4–metoxi–2–metilfenetil)–8–pentilbenzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–5–amina; (5–amino–2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–8–il)metanol; (5–amino–2–(4–

propoxifenetil)benzo[f][1,7]naftiridin–8–il)metanol; (2–(2–(1H–indol–5–il)etil)–5–aminobenzo[f][1,7]naftiridin–8–il)metanol; metil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N,3–dimetilbenzamida; N–(2–acetamidoetil)–4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N,3–dimetilbenzamida; 2–(4–metoxifenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N,N,3–trimetilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–hidroxietil)–3–metilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–3–metilbenzamida; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(pirrolidin–1–il)metanona; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dietilamino)etil)–3–metilbenzamida; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(4–etilpiperazin–1–il)metanona; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(piperazin–1–il)metanona; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metil–N–(2–(pirrolidin–1–il)etil)benzamida; 4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N,3–dimetilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N–metilbenzamida; 2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol; 2–(4–butoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(bifenil–4–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–((1,3–dihidroisobenzofuran–1–il)metil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(2–metilaliloxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(isopentiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–

metilbenzo[f][1,7]naftiridin–2–il)etil)fenil propil carbonato; etil 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)pentanoato; 2–(4–(ciclopentiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(ciclobutilmetoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(2–morfolinoetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)–1–feniletanona; ácido 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)pentanoico; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)etanol; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)–N,N–dimetilacetamida; 8–metil–2–(2–metil–4–(2–morfolinoetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etanol; dietil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propilfosfonato; ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propilfosfónico; 2–(4–butoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol; 2–(2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etanol; etil 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)pentanoato; ácido 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)pentanoico; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil etil carbonato; metil 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)butanoato; ácido 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)butanoico; ácido 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)butanoico; 2–(4–(isopentiloxi)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil hexil carbonato; 2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina; (5–amino–2–(2,4–

dimetilfenetil)benzo[f][1,7]naftiridin–8–il)metanol; dietil 3–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)propilfosfonato; dietil 3–(2–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etoxi)propilfosfonato; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil dimetilsulfamato; (5–amino–2–(4–(dimetilamino)fenetil)benzo[f][1,7]naftiridin–8–il)metanol; 2–(4–(dimetilamino)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol; 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona; 2–(4–((dimetilamino)metil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(1–(dimetilamino)etil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona oxima; 8–metil–2–(4–((metilamino)metil)fenetil)benzo[f][1,7]naftiridin–5–amina; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)bencilamino)etanol; 8–metil–2–(4–(pirrolidin–1–ilmetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(3,4–dimetoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)etanol; 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanol; 8–metil–2–(4–(oxazol–5–il)fenetil)benzo[f][1,7]naftiridin–5–amina; 3–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propanonitrilo; (2R)–2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propan–1–ol; 8–metil–2–(4–(1–(piperazin–1–il)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; ((2S)–1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidin–2–il)metanol; N^1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^2,N^2–dimetiletano–1,2–diamina; ácido 3–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propanoico; 8–metil–2–(4–(1–(4–metilpiperazin–1–il)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; N^2–(1–(4–(2–(5–

amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^1,N^1–dimetilpropano–1,2–diamina; 8–metil–2–(4–(1–(2–(piridin–4–il)etilamino)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; N^1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^2,N^2–dietiletano–1,2–diamina; 2–(4–(dimetilamino)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; ácido 1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidina–3–carboxílico; 4–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)fenol; 1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2 il)etil)fenil)etil)pirrolidin–3–ol; y 2–(4–(2–aminopropan–2–il)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

En ciertas realizaciones de los compuestos de Fórmula (XVI), o una de sus sales aceptables para uso farmacéutico, cada R^4, R^A y R^{13} se selecciona de manera independiente de H, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH_2OH$, $-OCH_3$, $-COOCH_3$, F, Cl, Br, $-CH_2OCH_3$, $-COOCH_2CH_3$, $CH_2OCH_2CH_3$, $-N(CH_3)_2$, $-((O(CH_2)_2)_{2\text{-}4}OH$, $-O(CH_2)_{2\text{-}4}-OH$, $-O(CH_2)_{2\text{-}4}-(PO_3H_2)$, $-O(CH_2)_{2\text{-}4}-COOH$, $-O(CH_2)_{2\text{-}4}-CH(CH_3)_2$, alquilo C_2–C_6 sustituido con 1-3 sustituyentes seleccionados de –OH, $-CH_3$, ciclopropilo, $-O(CH_2)_{2\text{-}4}-COOH$, $-O(CH_2)_{2\text{-}4}(PO_3H_2)$, –COOH, $COOCH_3$, y $-COOCH_2CH_3$. En otras realizaciones de los compuestos de Fórmula (XVI), R^4 es H. En otras realizaciones, dichos compuestos de Fórmula (XVI) tienen uno a tres grupos R^{13}. En otras realizaciones de dichos compuestos de Fórmula (XVI), R^A es H o Me. En otras realizaciones, dichos compuestos de Fórmula (XVI) tienen dos grupos R^{13} seleccionados del grupo integrado por $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH_2OH$, $-OCH_3$, $-COOCH_3$, $-COOCH_2CH_3$, F, Cl, Br, $-CH_2OCH_3$, $CH_2OCH_2CH_3$, $-N(CH_3)_2$, $-((O(CH_2)_2)_{2\text{-}4}OH$, $-O(CH_2)_{2\text{-}4}-OH$, $-O(CH_2)_{2\text{-}4}-(PO_3H_2)$, $-O(CH_2)_{2\text{-}4}-COOH$, $-O(CH_2)_{2\text{-}4}-CH(CH_3)_2$, alquilo C_2–C_6 sustituido con 1-3 sustituyentes seleccionados de –OH, $-CH_3$, ciclopropilo, $-O(CH_2)_{2\text{-}4}-COOH$, $-O(CH_2)_{2\text{-}4}(PO_3H_2)$, –COOH, $COOCH_3$, y

$-COOCH_2CH_3$. En otras realizaciones, dichos compuestos de Fórmula (XVI) están seleccionados de: 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol; 2–(4–metoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato de etilo; 2–(4–(dimetilamino)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina, y 2–(4–metoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

Otro aspecto proporcionado en esta solicitud lo constituyen composiciones farmacéuticas que comprenden una cantidad terapéuticamente eficaz de un compuesto de la Fórmula (I) como se describe con anterioridad y un portador aceptable para uso farmacéutico.

En ciertas realizaciones de este aspecto, la composición farmacéutica se formula para la administración intravenosa, la administración intravitrial, administración intramuscular, la administración oral, administración rectal, por inhalación, administración nasal, administración tópica, administración oftálmica o administración ótica. En otras realizaciones, las composiciones farmacéuticas se presentan en forma de un comprimido, una pastilla, una cápsula, un líquido, un inhalante, una solución para pulverización nasal, un supositorio, una solución, una emulsión, un ungüento, gotas oculares o gotas para el oído. En otras realizaciones, dichas composiciones farmacéuticas además incluyen uno o más agentes terapéuticos adicionales.

Otro aspecto proporcionado en la presente solicitud lo constituyen medicamentos para el tratamiento de una enfermedad o un trastorno en un paciente, donde está implicada la modulación de un receptor TLR, y dichos medicamentos comprenden una cantidad terapéuticamente eficaz de un compuesto de la Fórmula (I). En ciertas realizaciones de dichos medicamentos, el receptor TLR es TLR7. En otras realizaciones de dichos medicamentos, el

receptor TLR es TLR8. En ciertas realizaciones de dichos medicamentos, el compuesto es un agonista del receptor TLR. En ciertas realizaciones de dichos medicamentos, el compuesto es un agonista del receptor TLR7. En ciertas realizaciones de dichos medicamentos, el compuesto es un agonista del receptor TLR8.

Otro aspecto proporcionado en la presente solicitud comprende el uso de un compuesto de la Fórmula (I) en la elaboración de un medicamento para el tratamiento de una enfermedad o un trastorno en un paciente, donde está implicada la modulación de un receptor TLR.

Otro aspecto proporcionado en la presente solicitud comprende métodos para la modulación de un receptor TLR, donde los métodos comprenden la administración a un sistema o un sujeto que lo necesita, de una cantidad terapéuticamente eficaz de un compuesto de la Fórmula (I), o sus sales aceptables para uso farmacéutico o sus composiciones farmacéuticas, para, de ese modo, modular el receptor TLR. En ciertas realizaciones de dichos métodos, el receptor TLR es TLR7. En otras realizaciones de dichos métodos, el receptor TLR es TLR8. En ciertas realizaciones de dichos métodos, el compuesto es un agonista del receptor TLR. En ciertas realizaciones de dichos métodos, el compuesto es un agonista del receptor TLR7. En ciertas realizaciones de dichos métodos, el compuesto es un agonista del receptor TLR8. En ciertas realizaciones de dichos métodos, los métodos comprenden la administración del compuesto a una célula o un sistema de tejido o a un sujeto humano o animal.

En ciertas realizaciones de los métodos que se proporcionan en la presente solicitud para el tratamiento de un sujeto con respecto a una afección o un específico donde está implicado un TLR, dichos métodos además comprenden una etapa opcional de identificación de un sujeto que necesita dicho tratamiento.

Otro aspecto proporcionado en esta solicitud abarca métodos para el

tratamiento de una enfermedad o un trastorno donde está implicada la modulación de un receptor TLR, donde el método comprende la administración a un sistema o un sujeto que necesita dicho tratamiento, de una cantidad eficaz de un compuesto de la Fórmula (I), o de sus sales aceptables para uso farmacéutico, o sus composiciones, a fin de tratar, de ese modo la enfermedad o el trastorno. En ciertas realizaciones de dichos métodos, el receptor TLR es TLR7. En otras realizaciones de dichos métodos, el receptor TLR es TLR8. En ciertas realizaciones de dichos métodos, el compuesto es un agonista del receptor TLR. En ciertas realizaciones de dichos métodos, el compuesto es un agonista del receptor TLR7. En ciertas realizaciones de dichos métodos, el compuesto es un agonista del receptor TLR8. En ciertas realizaciones de dichos métodos, los métodos comprenden la administración del compuesto a una célula o un sistema de tejido, o a un sujeto humano o animal.

En ciertas realizaciones de dichos métodos, la enfermedad o la afección es una enfermedad infecciosa, una enfermedad inflamatoria, una enfermedad respiratoria, una enfermedad dermatológica o una enfermedad autoinmunitaria. En ciertas realizaciones de dichos métodos, la enfermedad o afección es asma, enfermedad pulmonar obstructiva crónica (EPOC), síndrome de insuficiencia respiratoria del adulto (ARDS, por sus siglas en inglés), colitis ulcerosa, enfermedad de Crohn, bronquitis, dermatitis, queratosis actínica, carcinoma de célula basal, rinitis alérgica, soriasis, esclerodermia, urticaria, artritis reumatoide, esclerosis múltiple, cáncer, cáncer de mama, HIV o lupus.

Otro aspecto proporcionado en la presente solicitud comprende métodos para el tratamiento de una enfermedad proliferativa celular, que comprende la administración a un sistema o a un sujeto que necesita dicho tratamiento, de una cantidad eficaz de un compuesto de la Fórmula (I), o de sus sales aceptables para uso farmacéutico, o de sus composiciones, donde la enfermedad proliferativa

celular es linfoma, osteosarcoma, melanoma o un tumor de mama, renal, próstata, colorrectal, tiroideo, ovárico, pancreático, neuronal, pulmonar, uterino o gastrointestinal.

Otro aspecto proporcionado en la presente solicitud lo comprenden composiciones farmacéuticas que incluyen un compuesto de la Fórmula (I) o (I–A), un antígeno y un portador aceptable para uso farmacéutico, donde dichas composiciones farmacéuticas son composiciones inmunógenas, y el compuesto es un potenciador inmunológico y se presenta en una cantidad eficaz para mejorar una respuesta inmunológica al antígeno, en un sujeto que recibe la composición. En ciertas realizaciones, dichas composiciones farmacéuticas además incluyen uno o más agentes inmunorreguladores. En ciertas realizaciones, los agentes inmunorreguladores comprenden uno o más coadyuvantes. En ciertas realizaciones, dichos coadyuvantes se seleccionan de coadyuvantes como una composición que contiene minerales, una emulsión oleosa, una formulación de saponina, un virosoma, una partícula de tipo viral, un derivado bacteriano, un derivado microbiano, un inmunomodulador humano, un bioadhesivo, un mucoadhesivo, una micropartícula, un liposoma, una formulación de polioxietileno éter, una formulación de polioxietileno éster, un polifosfazeno, un péptido de muramilo, o un compuesto de imidazoquinolona. En ciertas realizaciones, el coadyuvante es una emulsión oleosa. En ciertas realizaciones, las composiciones inmunógenas son útiles como vacunas, y el compuesto se presenta en una cantidad suficiente para producir un efecto inmunoestimulante con la administración.

Otro aspecto proporcionado en la presente solicitud comprende métodos para mejorar la eficacia de una composición inmunógena, que comprenden la adición de una cantidad eficaz de un compuesto de la Fórmula (I) o (I–A) a la composición inmunógena.

Otro aspecto presentado aquí son composiciones inmunogénicas que comprenden un compuesto de Fórmula (I-A), y un antígeno, donde la cantidad del compuesto es una cantidad efectiva para reforzar una respuesta inmune al antígeno en un sujeto al que se le administra la composición. En ciertas realizaciones de estas composiciones inmunogénicas, el antígeno es un antígeno bacteriano. En ciertas realizaciones de estas composiciones inmunogénicas, el antígeno bacteriano es un antígeno de una cepa de *Neisseria meningitides*. En otras realizaciones de estas composiciones inmunogénicas, el antígeno es un antígeno viral o un antígeno fúngico. En otras realizaciones, estas composiciones inmunogénicas comprenden además un adyuvante adicional. En ciertas realizaciones de estas composiciones inmunogénicas, el antígeno es un polipéptido. En ciertas realizaciones de estas composiciones inmunogénicas, el polipéptido posee al menos 85% de identidad con una secuencia seleccionada del grupo integrado por las SEC ID NOs: 1-6 que se proveen en la presente.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN.

Definiciones.

El término "alquenilo", de acuerdo con esta solicitud, se refiere a un hidrocarburo de cadena recta o ramificada, parcialmente insaturado, que tiene por lo menos un enlace doble de carbono–carbono. Los átomos orientados alrededor del enlace doble se encuentran en la conformación cis (Z) o trans (E). Un grupo alquenilo puede estar opcionalmente sustituido. De acuerdo con la presente solicitud, los términos "alquenilo C_2–C_3", "alquenilo C_2–C_4", "alquenilo C_2–C_5", "alquenilo C_2–C_6", "alquenilo C_2–C_7" y "alquenilo C_2–C_8" se refieren a un grupo alquenilo que contiene por lo menos 2, y como máximo, 3; 4; 5; 6; 7 u 8 átomos de carbono, respectivamente. A menos que se especifique lo contrario, un grupo alquenilo, en general, es un alquenilo C_2–C_6. Ejemplos no limitativos de grupos

alquenilo, de acuerdo con esta solicitud, incluyen etenilo, propenilo, butenilo, pentenilo, hexenilo, heptenilo, octenilo, nonenilo, decenilo y similares.

El término "alquenileno", de acuerdo con la presente solicitud, se refiere a un radical hidrocarburo divalente de cadena recta o ramificada, parcialmente insaturado, derivado de un grupo alquenilo. Un grupo alquenileno puede estar opcionalmente sustituido. De acuerdo con la presente solicitud, los términos "alquenileno C_2–C_3", "alquenileno C_2–C_4", "alquenileno C_2–C_5", "alquenileno C_2–C_6", "alquenileno C_2–C_7" y "alquenileno C_2–C_8" se refieren a un grupo alquenileno que contiene por lo menos 2, y como máximo, 3; 4; 5; 6; 7 u 8 átomos de carbono, respectivamente. A menos que se especifique lo contrario, un grupo alquenileno, en general, es un alquenileno C_1–C_6. Ejemplos no limitativos de grupos alquenileno de acuerdo con la presente solicitud incluyen etenileno, propenileno, butenileno, pentenileno, hexenileno, heptenileno, octenileno, nonenileno, decenileno y similares.

El término "alquilo", de acuerdo con la presente solicitud, se refiere a un hidrocarburo de cadena recta o ramificada saturado. Un grupo alquilo puede estar opcionalmente sustituido. De acuerdo con esta solicitud, los términos "alquilo C_1–C_3", "alquilo C_1–C_4", "alquilo C_1–C_5", "alquilo C_1–C_6", "alquilo C_1–C_7" y "alquilo C_1–C_8" se refieren a un grupo alquilo que contiene por lo menos 1, y como máximo, 3; 4; 5; 6; 7 u 8 átomos de carbono, respectivamente. A menos que se especifique lo contrario, un grupo alquilo, en genera, es un alquilo C_1–C_6. Ejemplos no limitativos de grupos alquilo como se usan en esta solicitud abarcan metilo, etilo, n–propilo, isopropilo, n–butilo, isobutilo, sec–butilo, t–butilo, n–pentilo, isopentilo, hexilo, heptilo, octilo, nonilo, decilo y similares

El término "alquileno", de acuerdo con la presente solicitud, se refiere a un radical hidrocarburo divalente de cadena recta o ramificada, saturado, derivado de un grupo alquilo. Un grupo alquileno puede estar opcionalmente sustituido. De

acuerdo con la presente solicitud, los términos "alquileno C_1–C_3", "alquileno C_1–C_4", "alquileno C_1–C_5", "alquileno C_1–C_6", "alquileno C_1–C_7" y "alquileno C_1–C_8" se refieren a un grupo alquileno que contiene por lo menos 1, y como máximo, 3; 4; 5; 6; 7 u 8 átomos de carbono, respectivamente. A menos que se especifique lo contrario, un grupo alquileno, en general, es un alquileno C_1–C_6. Ejemplos no limitativos de grupos alquileno como se usan en la presente solicitud incluyen metileno, etileno, n–propileno, isopropileno, n–butileno, isobutileno, sec–butileno, t–butileno, n–pentileno, isopentileno, hexileno y similares.

El término "alquinilo", de acuerdo con la presente solicitud, se refiere a un hidrocarburo de cadena recta o ramificada, parcialmente insaturado, que tiene por lo menos un enlace triple de carbono–carbono. Un grupo alquinilo puede estar opcionalmente sustituido. De acuerdo con la presente solicitud, los términos "alquinilo C_2–C_3", "alquinilo C_2–C_4", "alquinilo C_2–C_5", "alquinilo C_2–C_6", "alquinilo C_2–C_7" y "alquinilo C_2–C_8" se refieren a un grupo alquinilo que contiene por lo menos 2, y como máximo, 3; 4; 5; 6; 7 u 8 átomos de carbono, respectivamente. A menos que se especifique lo contrario, un grupo alquinilo, en general, es un alquinilo C_2–C_6. Ejemplos no limitativos de grupos alquinilo, de acuerdo con esta solicitud, incluyen etinilo, propinilo, butinilo, pentinilo, hexinilo, heptinilo, octinilo, noninilo, decinilo y similares.

El término "alquinileno", de acuerdo con la presente solicitud, se refiere a un radical hidrocarburo divalente de cadena recta o ramificada, parcialmente insaturado, derivado de un grupo alquinilo. Un grupo alquinileno puede estar opcionalmente sustituido. De acuerdo con la presente solicitud, los términos "alquinileno C_2–C_3", "alquinileno C_2–C_4", "alquinileno C_2–C_5", "alquinileno C_2–C_6", "alquinileno C_2–C_7" y "alquinileno C_2–C_8" se refieren a un grupo alquinileno que contiene por lo menos 2, y como máximo, 3; 4; 5; 6; 7 u 8 átomos de carbono, respectivamente. A menos que se especifique lo contrario, un grupo alquinileno,

en general, es un alquinileno C_2–C_6. Ejemplos no limitativos de grupos alquinileno de acuerdo con la presente solicitud incluyen etinileno, propinileno, butinileno, pentinileno, hexinileno, heptinileno, octinileno, noninileno, decinileno y similares.

El término "alcoxi," de acuerdo con la presente solicitud, se refiere al grupo –OR_a, donde R_a es un grupo alquilo como se define en esta solicitud. Un grupo alcoxi puede estar opcionalmente sustituido. De acuerdo con la presente solicitud, los términos "alcoxi C_1–C_3", "alcoxi C_1–C_4", "alcoxi C_1–C_5", "alcoxi C_1–C_6", "alcoxi C_1–C_7" y "alcoxi C_1–C_8" se refieren a un grupo alcoxi donde la porción alquilo contiene por lo menos 1, y como máximo, 3; 4; 5; 6; 7 u 8, átomos de carbono. Ejemplos no limitativos de grupos alcoxi de acuerdo con la presente solicitud incluyen metoxi, etoxi, n–propoxi, isopropoxi, n–butiloxi, t–butiloxi, pentiloxi, hexiloxi, heptiloxi, octiloxi, noniloxi, deciloxi y similares.

El término "arilo", de acuerdo con la presente solicitud, se refiere a sistemas de anillos monocíclicos, bicíclicos y tricíclicos que tienen un total de 5 a 14 miembros de anillo, donde por lo menos un anillo en el sistema es aromático, y donde cada anillo en el sistema contiene 3 a 7 miembros de anillo. Un grupo arilo puede estar opcionalmente sustituido. Ejemplos no limitativos de grupos arilo, de acuerdo con la presente solicitud, incluyen fenilo, naftilo, fluorenilo, indenilo, azulenilo, antracenilo y similares.

El término "arileno", de acuerdo con esta solicitud, significa un radical divalente derivado de un grupo arilo. Un grupo arileno puede estar opcionalmente sustituido.

El término "ciano", de acuerdo con la presente solicitud, se refiere a un grupo –CN.

El término "cicloalquilo", de acuerdo con la presente solicitud, se refiere a un montaje de anillos saturado o parcialmente insaturado, monocíclico, fusionado bicíclico, fusionado tricíclico o puenteado policíclico. De acuerdo con esta

solicitud, los términos "cicloalquilo C_3–C_5", "cicloalquilo C_3–C_6", "cicloalquilo C_3–C_7", "cicloalquilo C_3–C_8", "cicloalquilo C_3–C_9" y "cicloalquilo C_3–C_{10}" se refieren a un grupo cicloalquilo donde el montaje de anillos saturado o parcialmente insaturado, monocíclico, fusionado bicíclico o puenteado policíclico contiene por lo menos 3, y como máximo, 5; 6; 7; 8; 9 ó 10 átomos de carbono. Un grupo cicloalquilo puede estar opcionalmente sustituido. Ejemplos no limitativos de grupos cicloalquilo conforme a esta invención incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, ciclononilo, ciclodecilo, ciclopentenilo, ciclohexenilo, decahidronaftalenilo, 2,3,4,5,6,7–hexahidro–1H–indenilo y similares.

El término "halógeno", de acuerdo con esta solicitud, se refiere a flúor (F), cloro (Cl), bromo (Br), o yodo (I).

El término "halo", de acuerdo con la presente solicitud, se refiere a radicales halógeno: flúor (–F), cloro (–Cl), bromo (–Br) y yodo (–I).

Los términos "haloalquilo" o "alquilo sustituido con halo", o "alquilo halo–sustituido", de acuerdo con la presente invención, se refieren a un grupo alquilo como se define en esta solicitud, sustituido con uno o más grupos halógeno, donde los grupos halógeno son iguales o diferentes. Un grupo haloalquilo puede estar opcionalmente sustituido. Ejemplos no limitativos de dichos grupos haloalquilo de cadena recta o ramificada, de acuerdo con esta solicitud, incluyen metilo, etilo, propilo, isopropilo, isobutilo y n–butilo sustituidos con uno o más grupos halógeno, donde los grupos halógeno son iguales o diferentes, por ejemplo, sin limitación, trifluormetilo, pentafluoretilo y similares.

Los términos "haloalquenilo" o "alquenilo sustituido con halo", o "alquenilo halo–sustituido", de acuerdo con la presente invención, se refieren a un grupo alquenilo como se define en esta solicitud, sustituido con uno o más grupos halógeno, donde los grupos halógeno son iguales o diferentes. Un grupo

haloalquenilo puede estar opcionalmente sustituido. Ejemplos no limitativos de dichos grupos haloalquenilo de cadena recta o ramificada, de acuerdo con esta solicitud, incluyen etenilo, propenilo, butenilo, pentenilo, hexenilo, heptenilo, octenilo, nonenilo, decenilo y similares, sustituidos con uno o más grupos halógeno, donde los grupos halógeno son iguales o diferentes.

Los términos "haloalquinilo" o "alquinilo sustituido con halo", o "alquinilo halo–sustituido", de acuerdo con la presente invención, se refieren a un grupo alquinilo como se define anteriormente, sustituido con uno o más grupos halógeno, donde los grupos halógeno son iguales o diferentes. Un grupo haloalquinilo puede estar opcionalmente sustituido. Ejemplos no limitativos de dichos grupos haloalquinilo de cadena recta o ramificada, de acuerdo con esta solicitud, incluyen etinilo, propinilo, butinilo, pentinilo, hexinilo, heptinilo, octinilo, noninilo, decinilo y similares, sustituidos con uno o más grupos halógeno, donde los grupos halógeno son iguales o diferentes.

El término "haloalcoxi", como se usa en esta solicitud, se refiere a un grupo alcoxi como se define en esta solicitud, sustituido con uno o más grupos halógeno, donde los grupos halógeno son iguales o diferentes. Un grupo haloalcoxi puede estar opcionalmente sustituido. Ejemplos, sin limitación, de dichos grupos haloalcoxi de cadena recta o ramificada, de acuerdo con la presente invención, incluyen metoxi, etoxi, n–propoxi, isopropoxi, n–butiloxi, t–butiloxi, pentiloxi, hexiloxi, heptiloxi, octiloxi, noniloxi, deciloxi y similares, sustituidos con uno o más grupos halógeno, donde los grupos halógeno son iguales o diferentes.

El término "heteroalquilo", de acuerdo con la presente solicitud, se refiere a un grupo alquilo como se define en esta solicitud, donde uno o más átomos de carbono están reemplazados, de modo independiente, por uno o más de oxígeno, azufre, nitrógeno o sus combinaciones.

El término "heteroarilo", conforme a la presente invención, se refiere a sistemas de anillos monocíclicos, bicíclicos y tricíclicos que tienen un total de 5 a 14 miembros de anillo, donde por lo menos un anillo en el sistema es aromático, por lo menos un anillo en el sistema contiene uno o más heteroátomos seleccionados de nitrógeno, oxígeno y azufre; y donde cada anillo en el sistema contiene 3 a 7 miembros de anillo. Un grupo heteroarilo puede contener uno o más sustituyentes. Un grupo heteroarilo puede estar opcionalmente sustituido. Ejemplos, sin limitación, de grupos heteroarilo, de acuerdo con la presente invención, incluyen benzofuranilo, benzofurazanilo, benzoxazolilo, benzopiranilo, benztiazolilo, benzotienilo, benzazepinilo, bencimidazolilo, benzotiopiranilo, benzo[1,3]dioxol, benzo[b]furilo, benzo[b]tienilo, cinolinilo, furazanilo, furilo, furopiridinilo, imidazolilo, indolilo, indolizinilo, indolin–2–ona, indazolilo, isoindolilo, isoquinolinilo, isoxazolilo, isotiazolilo, 1,8–naftiridinilo, oxazolilo, oxaindolilo, oxadiazolilo, pirazolilo, pirrolilo, ftalazinilo, pteridinilo, purinilo, piridilo, piridazinilo, pirazinilo, pirimidinilo, quinoxalinilo, quinolinilo, quinazolinilo, 4H–quinolizinilo, tiazolilo, tiadiazolilo, tienilo, triazinilo, triazolilo y tetrazolilo.

El término "heterocicloalquilo", de acuerdo con la presente solicitud, se refiere a un cicloalquilo, como se define en esta solicitud, donde uno o más de los carbonos de anillo están reemplazados por una porción seleccionada de –O–, –N=, –NR–, –C(O)–, –S–, –S(O) – o –S(O)2–, donde R es hidrógeno, alquilo C_1–C_4 o un grupo protector de nitrógeno, con la condición de que el anillo de dicho grupo no contiene dos átomos O o S adyacentes. Un grupo heterocicloalquilo puede estar opcionalmente sustituido. Ejemplos no limitativos de grupos heterocicloalquilo, de acuerdo con esta invención, incluyen morfolino, pirrolidinilo, pirrolidinil–2–ona, piperazinilo, piperidinilo, piperidinilona, 1,4–dioxa–8–aza–spiro[4.5]dec–8–ilo, 2H–pirrolilo, 2–pirrolinilo, 3–pirrolinilo, 1,3–dioxolanilo, 2–imidazolinilo, imidazolidinilo, 2–pirazolinilo, pirazolidinilo, 1,4–dioxanilo, 1,4–

ditianilo, tiomorfolinilo, azepanilo, hexahidro–1,4–diazepinilo, tetrahidrofuranilo, dihidrofuranilo, tetrahidrotienilo, tetrahidropiranilo, dihidropiranilo, tetrahidrotiopiranilo, tioxanilo, azetidinilo, oxetanilo, tietanilo, oxepanilo, tiepanilo, 1,2,3,6–tetrahidropiridinilo, 2H–piranilo, 4H–piranilo, dioxanilo, 1,3–dioxolanilo, ditianilo, ditiolanilo, dihidropiranilo, dihidrotienilo, dihidrofuranilo, imidazolinilo, imidazolidinilo, 3–azabiciclo[3.1.0]hexanilo y 3–azabiciclo[4.1.0]heptanilo.

El término "heteroátomo", de acuerdo con la presente invención, se refiere a uno o más de oxígeno, azufre, nitrógeno, fósforo o silicio.

El término "hidroxilo", de acuerdo con la presente solicitud, se refiere al grupo –OH.

El término "hidroxialquilo", de acuerdo con la presente solicitud, se refiere a un grupo alquilo como se define en esta solicitud, sustituido con uno o más grupos hidroxilo. Ejemplos no limitativos de grupos hidroxialquilo C_1–C_6 de cadena recta o ramificada como se emplean en esta invención incluyen grupos metilo, etilo, propilo, isopropilo, isobutilo y n–butilo sustituidos con uno o más grupos hidroxilo.

El término "isocianato", conforme a la presente solicitud, se refiere a un grupo –N=C=O.

El término "isotiocianato", conforme a la presente solicitud, se refiere a un grupo –N=C=S.

El término "mercaptilo", de acuerdo con la presente solicitud, se refiere a un grupo (alquilo)S–.

El término "opcionalmente sustituido", de acuerdo con esta solicitud, significa que el grupo al que se hace referencia puede estar o no sustituido con uno o más grupos adicionales, seleccionados de manera individual e independiente de alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterocicloalquilo, hidroxilo, alcoxi, mercaptilo, ciano, halo, carbonilo, tiocarbonilo, isocianato, tiocianato, isotiocianato, nitro, perhaloalquilo, perfluoralquilo y amino,

que incluye grupos amino mono– y di–sustituidos, y sus derivados protegidos. Ejemplos no limitativos de sustituyentes opcionales comprenden halo, –CN, =O, =N–OH, =N–OR, =N–R, –OR, –C(O)R, –C(O)OR, –OC(O)R, –OC(O)OR, –C(O)NHR, $–C(O)NR_2$, –OC(O)NHR, $–OC(O)NR_2$, –SR–, –S(O)R, $–S(O)_2R$, –NHR, $–N(R)_2$, –NHC(O)R, –NRC(O)R, –NHC(O)OR, –NRC(O)OR, $S(O)_2NHR$, $–S(O)_2N(R)_2$, $–NHS(O)_2NR_2$, $–NRS(O)_2NR_2$, $–NHS(O)_2R$, $–NRS(O)_2R$, alquilo C_1–C_8, alcoxi C_1–C_8, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, alquilo C_1–C_8 sustituido con halo y alcoxi C_1–C_8 sustituido con halo, donde cada R se selecciona de modo independiente de H, halo, alquilo C_1–C_8, alcoxi C_1–C_8, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, alquilo C_1–C_8 sustituido con halo y alcoxi C_1–C_8 sustituido con halo. La colocación y la cantidad de dichos grupos sustituyentes se realizan de acuerdo con las limitaciones de valencia entendidas de cada grupo; por ejemplo, =O es un sustituyente adecuado para un grupo alquilo, si bien no lo es para un grupo arilo.

El término "solvato", de conformidad con la presente solicitud, se refiere a un complejo de variable estequiometría formado por un soluto (a modo de ejemplo, un compuesto de la Fórmula (I), o una de sus sales, como se describe en la presente solicitud) y un solvente. Ejemplos no limitativos de solventes son agua, acetona, metanol, etanol y ácido acético.

El término "aceptable", con respecto a una formulación, composición o un ingrediente, de conformidad con esta solicitud, significa que no tiene efecto nocivo persistente sobre la salud general del sujeto tratado.

El término "administración" del compuesto objeto significa la provisión de un compuesto de la Fórmula (I), o una de sus sales aceptables para uso farmacéutico, un solvato aceptable para uso farmacéutico, o uno de sus profármacos, a un sujeto que necesita tratamiento.

El término "cáncer", de acuerdo con la presente solicitud, se refiere a un

crecimiento anormal de células que tienden a proliferar de manera descontrolada, y en algunos casos, a hacer metástasis (diseminar). Los tipos de cáncer abarcan, sin limitación, tumores sólidos (tales como aquellos de la vejiga, el intestino, el cerebro, la mama, el endometrio, el corazón, riñón, pulmón, tejido linfático (linfoma), ovario, páncreas u otros órganos endocrinos (tiroides), la próstata, la piel (melanoma), o tumores hematológicos (tales como las leucemias).

El término "portador", de acuerdo con la presente solicitud, se refiere a compuestos químicos o agentes que facilitan la incorporación de un compuesto descripto en esta solicitud, en células o tejidos.

Los términos "coadministración" o "administración conjunta/combinada" o similares de acuerdo con la presente solicitud tienen la intención de contemplar la administración de los agentes terapéuticos seleccionados a un solo paciente, y tienen el propósito de incluir regímenes de tratamiento en los cuales los agentes no necesariamente se administran por la misma vía de administración o al mismo tiempo.

El término "trastorno dermatológico", de acuerdo con la presente solicitud, se refiere a un trastorno de la piel. Dichos trastornos dermatológicos abarcan, sin limitación, trastornos proliferativos o inflamatorios de la piel, tales como dermatitis atópica, trastornos vesiculares, enfermedad del tejido conjuntivo, dermatitis de contacto, eccema, enfermedad de Kawasaki, rosácea, síndrome de Sjogren–Larsso, queratosis actínica, carcinoma de célula basal y urticaria.

El término "diluyente", de acuerdo con la presente solicitud, se refiere a compuestos químicos que se usan a fin de diluir un compuesto descripto en la presente solicitud antes de la administración. Los diluyentes además pueden usarse para estabilizar compuestos descriptos en esta solicitud.

Los términos "cantidad eficaz" o "cantidad terapéuticamente eficaz", como se usan en la presente solicitud, se refieren a una cantidad suficiente de un

compuesto descripto en esta solicitud administrado, que aliviará a cierto alcance uno o más de los síntomas de la enfermedad o afección tratada. El resultado puede ser la reducción o el alivio de los signos, los síntomas o las causas de una enfermedad, o cualquier otra alteración deseada de un sistema biológico. Por ejemplo, una "cantidad eficaz" para usos terapéuticos es la cantidad de la composición que comprende un compuesto como se revela en esta solicitud, necesaria para proporcionar una disminución clínicamente significativa en los síntomas de la enfermedad. Una cantidad "eficaz" apropiada, en cualquier caso individual, puede ser determinada usando técnicas, tales como un estudio de escala de dosis.

Los términos "mejorar" o "mejoría", de acuerdo con la presente solicitud, significan el incremento o la prolongación, ya sea en la potencia, ya sea en la duración, de un efecto deseado. En consecuencia, con respecto a la mejoría del efecto de agentes terapéuticos, el término "mejorar" se refiere a la capacidad para incrementar o prolongar, ya sea la potencia, ya sea la duración, del efecto de otros agentes terapéuticos en un sistema. Una "cantidad eficaz para la mejoría", de acuerdo con la presente solicitud, se refiere a una cantidad adecuada para mejorar el efecto de otro agente terapéutico en un sistema deseado.

Los términos "fibrosis" o "trastorno fibroso", de acuerdo con la presente solicitud, se refieren a afecciones que siguen a la inflamación aguda o crónica y que se asocian con la acumulación anormal de células o colágeno, e incluyen, sin limitación, fibrosis de tejidos u órganos individuales tales como el corazón, el riñón, las articulaciones, el pulmón o la piel, y abarcan trastornos como fibrosis pulmonar idiopática y alveolitis fibrosa criptógena.

El término "iatrogénico", de acuerdo con la presente solicitud, significa una afección, un trastorno o una enfermedad creados o empeorados por el tratamiento médico o quirúrgico.

El término "cantidad inmunológicamente eficaz", de acuerdo con la presente solicitud, significa la administración de una cantidad suficiente a un individuo, ya sea en una sola dosis, ya sea como parte de una serie, eficaz para el tratamiento o la prevención de un trastorno o una enfermedad inmunológica. Esta cantidad varía de acuerdo con la salud y el estado físico del individuo por tratar, la edad, el grupo taxonómico del individuo por tratar (por ejemplo, primate no humano, primate, etc.), la capacidad del sistema inmunológico del individuo para sintetizar anticuerpos, el grado de protección deseado, la formulación de la vacuna, la evaluación médica del tratamiento de la situación clínica y otros factores pertinentes. Se espera que la cantidad se encuentre dentro de un rango relativamente amplio que puede ser determinado a través de ensayos de rutina.

El término "trastornos inflamatorios", de acuerdo con la presente solicitud, se refiere a aquellas enfermedades o afecciones que se caracterizan por uno o más de los signos de dolor (a partir de la generación de sustancias nocivas y la estimulación de nervios), calor (por la vasodilatación), enrojecimiento (rubor, por la vasodilatación y el mayor flujo sanguíneo), hinchazón (tumor, por la excesiva afluencia o el restringido efluente de fluido) y la pérdida de función (*functio laesa*, que puede ser parcial o completa, temporal o permanente). La inflamación adopta muchas formas, y abarca, sin limitación, la inflamación representada por una o más de las siguientes: aguda, adhesiva, atrófica, catarral, crónica, cirrótica, difusa, diseminada, exudativa, fibrinosa, fibrosa, focal, granulomatosa, hiperplásica, hipertrófica, intersticial, metastásica, necrótica, obliterada, parenquimatosa, plásica, productiva, proliferativa, pseudomembranosa, purulenta, esclerosante, seroplásica, serosa, simple, específica, subaguda, supurativa, tóxica, traumática o ulcerosa. Los trastornos inflamatorios además incluyen, sin limitación, aquellos que afectan los vasos sanguíneos (poliarteritis, artritis temporal); las articulaciones (artritis; cristalina, artrosis, psoriásica, reactiva, reumatoide, de Reiter); el tracto

gastrointestinal (enfermedad); la piel (dermatitis); o múltiples órganos y tejidos (lupus eritematoso sistémico).

El término "modular", de acuerdo con la presente solicitud, significa la interacción con un blanco, ya sea directa, ya sea indirectamente, de modo de alterar la actividad del blanco, que incluye, solo a modo de ejemplo, la mejoría de la actividad del blanco, la inhibición de la actividad del blanco, la limitación de la actividad del blanco, o la extensión de la actividad del blanco.

El término "modulador", de acuerdo con la presente solicitud, se refiere a una molécula que interactúa con un blanco, ya sea directamente, ya sea indirectamente. Las interacciones incluyen, sin limitación, las interacciones de un agonista o un antagonista.

Los términos "enfermedad ocular" o "enfermedad oftálmica", de acuerdo con la presente solicitud, se refieren a enfermedades que afectan los ojos y potencialmente los tejidos circundantes. Las enfermedades oculares u oftálmicas incluyen, sin limitación, conjuntivitis, retinitis, escleritis, uveítis, conjuntivitis alérgica, conjuntivitis primaveral, conjuntivitis papilar y retinitis por citomegalovirus (CMV).

El término "farmacéuticamente aceptable" o "aceptable para uso farmacéutico", de acuerdo con esta solicitud, se refiere a un material, tal como un portador o diluyente, que no anula la actividad biológica o las propiedades de los compuestos que aquí se describen. Dichos materiales se administran a un individuo sin causar efectos biológicos indeseables o interactuar de manera nociva con cualquiera de los componentes de la composición en la cual están contenidos.

El término "sal farmacéuticamente aceptable", de acuerdo con esta solicitud, se refiere a una formulación de un compuesto que no causa irritación significativa en un organismo al cual se administra, y no anula la actividad

biológica y las propiedades de los compuestos que aquí se describen.

Los términos "combinación" o "combinación farmacéutica", de acuerdo con la presente solicitud, significan un producto que resulta de la mezcla o combinación de más de un ingrediente activo, e incluyen tanto combinaciones fijas como no fijas de los ingredientes activos. El término "combinación fija" significa que los ingredientes activos, a modo de ejemplo, un compuesto de la Fórmula (I) y un agente terapéutico adicional, se administran ambos a un paciente en forma simultánea, en forma de una sola entidad o dosificación. El término "combinación no fija" significa que los ingredientes activos, a modo de ejemplo, un compuesto de la Fórmula (I) y un agente terapéutico adicional, se administran ambos a un paciente como entidades separadas, ya sea en forma simultánea, ya sea en forma concurrente o sucesiva, sin límites de tiempo específicos, donde dicha administración proporciona niveles terapéuticamente eficaces de los dos compuestos en el organismo del paciente. Esto además se aplica a tratamientos de cócteles, por ejemplo, la administración de 3 o más ingredientes activos.

Los términos "composición" o "composición farmacéutica" de acuerdo con la presente solicitud se refieren a por lo menos un compuesto tal como los compuestos de la Fórmula (I) descriptos en esta solicitud, con por lo menos uno, y opcionalmente, más de un componente químico farmacéuticamente aceptable, por ejemplo, portadores, estabilizadores, diluyentes, agentes de dispersión, agentes de suspensión, agentes espesadores o excipientes.

El término "profármaco", de acuerdo con la presente solicitud, se refiere a un agente que es convertido en el fármaco original *in vivo*. Un ejemplo no limitativo de un profármaco de los compuestos que aquí se describen es un compuesto descripto en esta solicitud, administrado como un éster, que luego es metabólicamente hidrolizado hasta un ácido carboxílico, la entidad activa, una vez dentro de la célula. Un ejemplo adicional de un profármaco es un péptido corto

enlazado a un grupo ácido, donde el péptido es metabolizado a fin de revelar la porción activa.

El término "enfermedad respiratoria", de acuerdo con la presente solicitud, se refiere a enfermedades que afectan los órganos, involucrados en la respiración, tales como la nariz, la garganta, laringe, tráquea, los bronquios y pulmones. Las enfermedades respiratorias abarcan, sin limitación, asma, síndrome de insuficiencia respiratoria del adulto y asma alérgica (extrínseca), asma no alérgica (intrínseca), asma severa aguda, asma crónica, asma clínica, asma nocturna, asma inducida por alergenos, asma sensible a la aspirina, asma inducida por el ejercicio, hiperventilación isocápnica, asma de inicio en la niñez, asma de inicio en la adultez, asma con variante de tos, asma ocupacional, asma resistente a corticoesteroides, asma estacional, rinitis alérgica estacional, rinitis alérgica, enfermedad pulmonar obstructiva crónica, que incluye bronquitis crónica o enfisema, hipertensión pulmonar, fibrosis pulmonar intersticial o inflamación de las vías respiratorias y fibrosis quística e hipoxia.

El término "sujeto" o "paciente", de acuerdo con la presente solicitud, contempla mamíferos y no mamíferos. Ejemplos de mamíferos comprenden, sin limitación, seres humanos, chimpancés, simios, monos, vacas, caballos, ovejas, cabras, cerdos, conejos, perros, gatos, ratas, ratones, cobayas y similares. Ejemplos de no mamíferos abarcan, sin limitación, aves, peces y similares. Con frecuencia, el sujeto es un ser humano, y puede ser un ser humano que ha sido diagnosticado y necesita tratamiento de una enfermedad o de un trastorno aquí descriptos.

El término "modulador de TLR", de acuerdo con la presente solicitud, se refiere a un compuesto que modula un receptor TLR.

Los términos "enfermedad de TLR" o "una enfermedad o un trastorno asociados con la actividad de TLR", de acuerdo con la presente solicitud, se

refieren a cualquier enfermedad asociada con un receptor de tipo toll. Dichas enfermedades o dichos trastornos incluyen, sin limitación, enfermedades infecciosas, enfermedades inflamatorias, enfermedades respiratorias y enfermedades autoinmunitarias, tales como, solo a modo de ejemplo, asma, enfermedad pulmonar obstructiva crónica (EPOC), síndrome de insuficiencia respiratoria del adulto (ARD), enfermedad de Crohn, bronquitis, dermatitis, rinitis alérgica, psoriasis, esclerodermia, urticaria, artritis reumatoide, esclerosis múltiple, cáncer, HIV y lupus.

El término "cantidad terapéuticamente eficaz", de acuerdo con la presente solicitud, se refiere a una cantidad de un compuesto que, en comparación con un sujeto correspondiente que no ha recibido dicha cantidad, logra mejor tratamiento, sanación, prevención o mejoría de una enfermedad, un trastorno o efecto colateral, o una disminución de la velocidad de avance de una enfermedad o de un trastorno. El término además incluye, dentro de su alcance, cantidades eficaces para mejorar la función fisiológica normal.

Los términos "tratar" o "tratamiento", de conformidad con la presente solicitud, se refieren a métodos para el alivio, la mitigación o la mejoría de los síntomas de una enfermedad o afección; la prevención de síntomas adicionales; la mejoría o la prevención de causas metabólicas subyacentes de los síntomas; la inhibición de la enfermedad o afección; la detención del desarrollo de la enfermedad o afección; el alivio de la enfermedad o afección; el logro de la regresión de la enfermedad o afección; el alivio de una afección causada por la enfermedad o afección; o la detención de los síntomas de la enfermedad o afección, ya sea en forma profiláctica, ya sea en forma terapéutica.

Otros objetivos, características y ventajas de los métodos, las composiciones y las combinaciones que aquí se describen serán evidentes a partir de la siguiente descripción detallada. Debe entenderse, sin embargo, que si

bien indican realizaciones específicas, la descripción detallada y los ejemplos específicos se proporcionan solo a modo de ilustración.

Breve descripción de las Figuras

La Figura 1 muestra los resultados del título de anticuerpo bactericida sérico ("SBA") determinado dos semanas después de la segunda dosis utilizando el método CFU estándar o e método de Azul Alamar utilizando una cepa de serogrupo NZ98 de N. meningitidis (con la dosis del compuesto en µg indicado a la izquierda. El cambio en veces sobre la respuesta ejercida con MF59/3MenB se muestra a la derecha de cada barra.

La Figura 2 muestra el resultado promedio de tres estudios SBA independientes. la desviación estándar se muestra como barras de error. Los títulos de SBA se midieron en todos los casos utilizando el método CFY estándar. La dosis de cada compuesto se indica a la izquierda en µg.

La Figura 3 muestra los títulos de SBA de dos estudios independientes que comparan la respuesta a dosis del ejemplo No. 47 con 3MenB adyuvada con alum en lugar del adyuvante MF59.

La Figura 4 muestra los títulos de SBA de otro estudio que compara la respuesta a dosis de otro compuesto, Ejemplo No. 169.

La Figura 5 resume la información de seis experimentos totales. ** y * sobre el compuesto indican una diferencia en el valor p estadísticamente significativa entre la inmunización con el compuesto y la inmunización sin el compuesto (es decir, en

comparación con el control 3MenB/MF59). "NS" indica que la diferencia no fue estadísticamente significativa para el valor p.

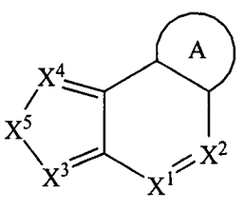
Descripción de las realizaciones preferidas.

Se proveen en la presente solicitud compuestos y sus composiciones farmacéuticas, que son moduladores de receptores de tipo toll (TLR). En ciertas realizaciones, ciertos compuestos descriptos en esta solicitud y sus composiciones farmacéuticas son agonistas de receptores de tipo toll. En otras realizaciones, dichos compuestos y sus composiciones farmacéuticas son agonistas de TLR7. En otras realizaciones, dichos compuestos y sus composiciones farmacéuticas son agonistas de TLR8. En otras realizaciones, dichos compuestos y sus composiciones farmacéuticas son agonistas tanto de TLR7 como de TLR8, es decir, que dichos compuestos y sus composiciones farmacéuticas son agonistas duales de TLR7 y TLR8.

Se proveen en la presente solicitud compuestos, composiciones farmacéuticas y métodos para el tratamiento o la prevención de enfermedades o trastornos asociados con la actividad de TLR. En ciertas realizaciones, dichos TLR son TLR7 y TLR8.

Los moduladores de TLR proporcionados en la presente solicitud incluyen compuestos que tienen la estructura de la Fórmula (I) y sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros.

Se proporcionan en la presente solicitud compuestos, sales aceptables para uso farmacéutico, solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), derivados de N–óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezclas de sus isómeros, que tienen la estructura de la Fórmula (I):



Fórmula (I)

donde:

X^1 es N o $CN(R^1R^2)$; X^2 es N o $CN(R^1R^2)$, siempre que cuando X^1 es $CN(R^1R^2)$, entonces X^2 es N;

X^3 es N o CR^6;

X^4 es N o CR^3; y X^5 es $-CR^4=CR^5-$, $-CR^4=N-$ o $-N=CR^5-$;

R^1 y R^2 se seleccionan, de manera independiente, de H, $-C(O)R^8$, alquilo C_1-C_6, heteroalquilo C_1-C_6, haloalquilo C_1-C_6, arilo, heteroarilo, cicloalquilo C_3-C_8 y heterocicloalquilo C_3-C_8;

donde los grupos alquilo C_1-C_6, heteroalquilo C_1-C_6, haloalquilo C_1-C_6, cicloalquilo C_3-C_8 o heterocicloalquilo C_3-C_8 de R^1 y R^2, de modo independiente, están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de modo independiente de halógeno, –CN, =O, alquilo C_1-C_6, haloalquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_8, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-C(O)N(R^9)_2$, heterocicloalquilo C_3-C_8, $-S(O)_2R^8$, $-S(O)_2\ N(R^9)_2$, $-N\ R^9S(O)_2R^8$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$, $-OLP(O)(OR^{10})_2$, haloalquilo C_1-C_6 y haloalcoxi C_1-C_6; y

donde los grupos arilo y heteroarilo de R^1 y R^2, de manera independiente, están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de modo independiente de halógeno, –CN, alquilo C_1-C_6, haloalquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_8, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-C(O)N(R^9)_2$, heterocicloalquilo C_3-C_8, $-S(O)_2R^8$, $-S(O)_2\ N(R^9)_2$, $-N\ R^9S(O)_2R^8$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$, $-OLP(O)(OR^{10})_2$, haloalquilo C_1-C_6 y haloalcoxi C_1-C_6;

o R^1 y R^2 son, de manera independiente, alquilo C_1–C_6 que puede estar sustituido como se describe con anterioridad, y tomados junto con el átomo de N al cual están unidos, forman un heterocicloalquilo C_3–C_8 opcionalmente sustituido;

R^3 y R^6 se seleccionan, de modo independiente, de H, halógeno, alquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alcoxi C_1–C_6, haloalcoxi C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8;

donde los grupos alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alcoxi C_1–C_6, haloalcoxi C_1–C_6, cicloalquilo C_3–C_8, o heterocicloalquilo C_3–C_8 de R^3 y R^6, de manera independiente, están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de modo independiente de halógeno, –CN, =O, R^7, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-C(O)N(R^9)_2$, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$ y $-NR^9S(O)_2R^8$; y

donde los grupos arilo y heteroarilo de R^3 y R^6 de modo independiente están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de manera independiente de halógeno, –CN, R^7, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-C(O)N(R^9)_2$, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$ y $-NR^9S(O)_2R^8$;

R^4 y R^5 se seleccionan independientemente de H, halógeno, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-SR^7$, $-(CH_2)_nOR^7$, $-(CH_2)_nR^7$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8;

donde los grupos alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6, cicloalquilo C_3–C_8 o heterocicloalquilo C_3–C_8 de R^4 y R^5 de manera independiente están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de modo independiente de halógeno, –CN, =O, $-NO_2$, $-R^7$, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$,

$-C(O)OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-C(O)N(R^9)_2$, $-Si(R^8)_3$, $-S(O)_2R^8$, $-S(O)R^8$, $-S(O)_2\,N(R^9)_2$ y $-N\,R^9S(O)_2R^8$, y

donde los grupos arilo y heteroarilo de R^4 y R^5, de manera independiente, están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de modo independiente de halógeno, $-CN$, $-R^7$, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-C(O)N(R^9)_2$, $-Si(R^8)_3$, $-S(O)_2R^8$, $-S(O)R^8$, $-S(O)_2\,N(R^9)_2$ y $-N\,R^9S(O)_2R^8$;

o R^3 y R^4, o R^4 y R^5, o R^5 y R^6, cuando se presentan en átomos de anillos adyacentes, pueden estar opcionalmente unidos para formar un anillo de 5–6 miembros; donde el anillo de 5-6 miembros está opcionalmente sustituido con R^7;

cada L se selecciona de manera independiente de un enlace, $-(O(CH_2)_m)_t-$, alquilo C_1–C_6, alquenileno C_2–C_6 y alquinileno C_2–C_6, donde los alquilo C_1–C_6, alquenileno C_2–C_6 y alquinileno C_2–C_6 de L están, cada uno, opcionalmente sustituidos con 1 a 4 sustituyentes seleccionados independientemente de halógeno, $-R^8$, $-OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, y $-OP(O)(OR^{10})_2$;

R^7 se selecciona de H, alquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6 y heterocicloalquilo C_3–C_8;

donde los grupos alquilo C_1–C_6, cicloalquilo C_3–C_8, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6, o heterocicloalquilo C_3–C_8 de R^7 están, de modo independiente, opcionalmente sustituidos con 1 a 3 grupos R^{13}, y cada R^{13} se selecciona de modo independiente de halógeno, $-CN$, $=O$, $-LR^9$, $-LOR^9$, $-OLR^9$, $-LR^{10}$, $-LOR^{10}$, $-OLR^{10}$, $-LR^8$, $-LOR^8$, $-OLR^8$, $-LSR^8$, $-LSR^{10}$, $-LC(O)R^8$, $-OLC(O)R^8$, $-LC(O)OR^8$, $-LC(O)R^{10}$, $-LOC(O)OR^8$, $-LC(O)NR^9R^{11}$, $-LC(O)NR^9R^8$, $-LN(R^9)_2$, $-LNR^9R^8$, $-LNR^9R^{10}$, $-LC(O)N(R^9)_2$, $-LS(O)_2R^8$, $-LS(O)R^8$, $-LC(O)NR^8OH$, $-LNR^9C(O)R^8$,

$-LNR^9C(O)OR^8$, $-LC(=N-OR^8)R^8$, $-LC(=NH)-NHOR^8$, $-NHC(=NH)NH_2$, $-LS(O)_2N(R^9)_2$, $-OLS(O)_2N(R^9)_2$, $-LNR^9S(O)_2R^8$, $-LC(O)NR^9LN(R^9)_2$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$ y $-OLP(O)(OR^{10})_2$;

donde los grupos arilo y heteroarilo de R^7 están, cada uno, opcionalmente sustituidos con 1 a 3 grupos R^{13}, y cada R^{13} se selecciona de manera independiente de halógeno, $-CN$, $-LR^9$, $-LOR^9$, $-OLR^9$, $-LR^{10}$, $-LOR^{10}$, $-OLR^{10}$, $-LR^8$, $-LOR^8$, $-OLR^8$, $-LSR^8$, $-LSR^{10}$, $-LC(O)R^8$, $-OLC(O)R^8$, $-LC(O)OR^8$, $-LC(O)R^{10}$, $-LOC(O)OR^8$, $-LC(O)NR^9R^{11}$, $-LC(O)NR^9R^8$, $-LN(R^9)_2$, $-LNR^9R^8$, $-LNR^9R^{10}$, $-LC(O)N(R^9)_2$, $-LS(O)_2R^8$, $-LS(O)R^8$, $-LC(O)NR^8OH$, $-LNR^9C(O)R^8$, $-LNR^9C(O)OR^8$, $-LC(=N-OR^8)R^8$, $-LC(=NH)-NHOR^8$, $-NHC(=NH)NH_2$, $-LS(O)_2N(R^9)_2$, $-OLS(O)_2N(R^9)_2$, $-LNR^9S(O)_2R^8$, $-LC(O)NR^9LN(R^9)_2$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$ y $-OLP(O)(OR^{10})_2$;

cada R^8 se selecciona de manera independiente de H, $-CH(R^{10})_2$, alquilo C_1–C_8, alqueno C_2–C_8, alquino C_2–C_8, haloalquilo C_1–C_6, alcoxi C_1–C_6, heteroalquilo C_1–C_6, cicloalquilo C_3–C_8, heterocicloalquilo C_2–C_8, hidroxialquilo C_1–C_6, y haloalcoxi C_1–C_6, donde los grupos alquilo C_1–C_8, alqueno C_2–C_8, alquino C_2–C_8, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alcoxi C_1–C_6, cicloalquilo C_3–C_8, heterocicloalquilo C_2–C_8, hidroxialquilo C_1–C_6 y haloalcoxi C_1–C_6 de R^8 están, cada uno, opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente de $-CN$, R^{11}, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-OC(O)R^{11}$, $-C(O)N(R^9)_2$, $-C(O)OR^{11}$, $-NR^9C(O)R^{11}$, $-NR^9R^{10}$, $-NR^{11}R^{12}$, $-N(R^9)_2$, $-OR^9$, $-OR^{10}$, $-C(O)NR^{11}R^{12}$, $-C(O)NR^{11}OH$, $-S(O)_2R^{11}$, $-S(O)R^{11}$, $-S(O)_2NR^{11}R^{12}$, $-NR^{11}S(O)_2R^{11}$, $-P(O)(OR^{11})_2$, y $-OP(O)(OR^{11})_2$;

cada R^9 se selecciona de manera independiente de H, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-Si(R^8)_3$, $-S(O)_2R^{10}$, alquilo C_1–C_6, heteroalquilo C_1–C_6 y cicloalquilo C_3–C_6; o cada R^9 es independientemente un alquilo C_1–C_6 que junto con N se unen para formar un heterocicloalquilo C_3–C_8, donde el anillo

heterocicloalquilo C_3–C_8 contiene opcionalmente un heteroátomo adicional seleccionado de N, O y S, y donde los grupos alquilo C_1–C_6, heteroalquilo C_1–C_6, cicloalquilo C_3–C_6, o heterocicloalquilo C_3–C_8 de R^9 están, cada uno, opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente de –CN, R^{11}, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-OC(O)R^{11}$, $-C(O)OR^{11}$, $-NR^{11}R^{12}$, $-C(O)NR^{11}R^{12}$, $-C(O)NR^{11}OH$, $-S(O)_2R^{11}$, $-S(O)R^{11}$, $-S(O)_2NR^{11}R^{12}$, $-NR^{11}S(O)_2R^{11}$, $-P(O)(OR^{11})_2$, y $-OP(O)(OR^{11})_2$;

cada R^{10} se selecciona de manera independiente de arilo, cicloalquilo C_3–C_8, heterocicloalquilo C_3–C_8 o un heteroarilo, donde los grupos arilo, cicloalquilo C_3–C_8, heterocicloalquilo C_3–C_8 o heteroarilo están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de halógeno, $-R^8$, $-OR^8$, $-LR^9$, $-LOR^9$,$-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9CO_2R^8$, $-CO_2R^8$, $-C(O)R^8$ y $-C(O)N(R^9)_2$;

R^{11} y R^{12} se seleccionan de modo independiente de H, alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8;

donde los grupos alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, cicloalquilo C_3–C_8 o heterocicloalquilo C_3–C_8 de R^{11} y R^{12}, de manera independiente, están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de modo independiente de halógeno, –CN, =O, R^8, $-OR^8$, $-C(O)R^8$, $^-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-NR^8C(O)R^8$, $-NR^8C(O)OR^8$, $-C(O)N(R^9)_2$, heterocicloalquilo C_3–C_8, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, $-NR^9S(O)_2R^8$, haloalquilo C_1–C_6 y haloalcoxi C_1–C_6; y

donde los grupos arilo y heteroarilo de R^{11} y R^{12} de manera independiente están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de modo independiente de halógeno, –CN, R^8, $-OR^8$, $-C(O)R^8$, $^-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-NR^8C(O)R^8$, $-NR^8C(O)OR^8$,$-C(O)N(R^9)_2$, heterocicloalquilo C_3–C_8, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, $-NR^9S(O)_2R^8$, haloalquilo C_1–C_6 y haloalcoxi C_1–C_6;

o R^{11} y R^{12} son, de manera independiente, alquilo C_1–C_6, y tomados junto con el átomo de N al cual están unidos forman un heterocicloalquilo C_3–C_8 opcionalmente sustituido que contiene opcionalmente un heteroátomo adicional seleccionado de N, O y S;

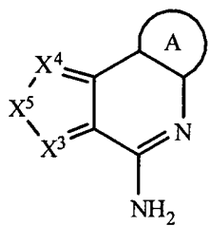
el anillo A es un arilo o un heteroarilo, donde los grupos arilo o heteroarilo del anillo A están opcionalmente sustituidos con 1 a 3 grupos R^A, donde cada R^A se selecciona de modo independiente de halógeno, $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, $-CN$, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$ y $-(CH_2)_nNHC(O)R^8$, y dos sustituyentes adyacentes en el anillo A pueden unirse para formar un anillo de 5–6 miembros que contiene hasta dos heteroátomos como miembros de anillo; y

n es, de modo independiente en cada aparición, 0; 1; 2; 3; 4; 5; 6; 7 u 8;

cada m se selecciona de manera independiente de 1, 2, 3, 4, 5 y 6, y

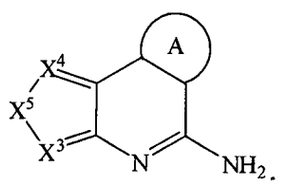
t es 1, 2, 3, 4, 5, 6, 7 u 8.

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, sus solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), los derivados de N–óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezclas de sus isómeros tienen la estructura de la Fórmula (I–A):



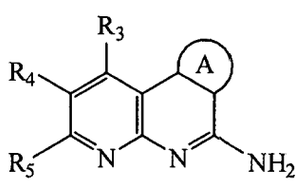
Fórmula (I–A).

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, sus solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), los derivados de N–óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezclas de sus isómeros tienen la estructura de la Fórmula (I–B):



Fórmula (I–B).

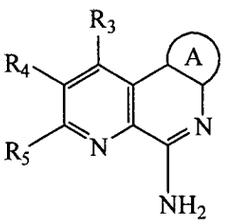
En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, sus solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), los derivados de N–óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezclas de sus isómeros tienen la estructura de la Fórmula (II):



Fórmula (II).

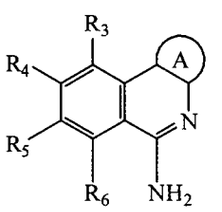
En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, sus solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), los derivados de N–óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezclas de sus isómeros tienen la

estructura de la Fórmula (III):



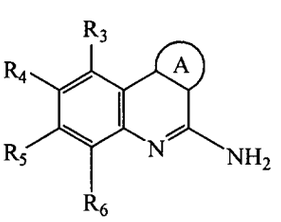
Formula (III).

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, sus solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), los derivados de N–óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezclas de sus isómeros tienen la estructura de la Fórmula (IV):



Fórmula (IV).

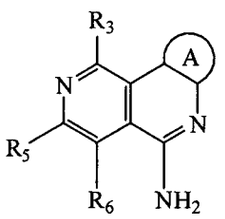
En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, sus solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), los derivados de N–óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezclas de sus isómeros tienen la estructura de la Fórmula (V),



Fórmula (V).

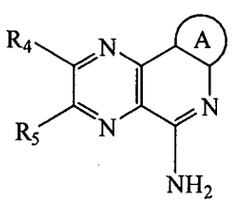
En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, sus solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), los derivados de N–óxido, derivados de profármacos,

derivados protegidos, isómeros individuales y mezclas de sus isómeros tienen la estructura de la Fórmula (VI):



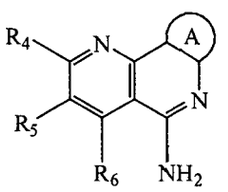
Fórmula (VI).

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, sus solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), los derivados de N–óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezclas de sus isómeros tienen la estructura de la Fórmula (VII):



Fórmula (VII).

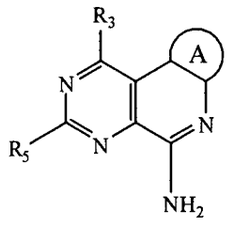
En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, sus solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), los derivados de N–óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezclas de sus isómeros tienen la estructura de la Fórmula (VIII):



Fórmula (VIII).

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, sus solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), los derivados de N–óxido, derivados de profármacos,

derivados protegidos, isómeros individuales y mezclas de sus isómeros tienen la estructura de la Fórmula (IX):



Fórmula (IX).

En ciertas realizaciones de los compuestos de las Fórmulas (I)–(IX), la Fórmula (I–A) y la Fórmula (I–B), el anillo A se selecciona de fenilo, naftilo, fluorenilo, indenilo, azulenilo y antracenilo, cada uno de los cuales está opcionalmente sustituido con 1 a 3 grupos R^A, donde cada R^A se selecciona de manera independiente de $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, $-CN$, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$ y $-(CH_2)_nNHC(O)R^8$. En otras realizaciones de los compuestos de las Fórmulas (I)–(IX), la Fórmula (I–A) y la Fórmula (I–B), el anillo A es fenilo o naftilo, cada uno de los cuales está opcionalmente sustituido con 1 a 3 grupos R^A, donde cada R^A se selecciona de manera independiente de $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, $-CN$, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$,

$-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$ y $-(CH_2)_nNHC(O)R^8$.

En ciertas realizaciones de los compuestos de las Fórmulas (I)–(IX), la Fórmula (I–A) y la Fórmula (I–B), el anillo A se selecciona de benzofuranilo, benzofurazanilo, benzoxazolilo, benzopiranilo, benztiazolilo, benzotienilo, benzazepinilo, bencimidazolilo, benzotiopiranilo, benzo[1,3]dioxol, benzo[b]furilo, benzo[b]tienilo, cinolinilo, furazanilo, furilo, furopiridinilo, imidazolilo, indolilo, indolizinilo, indolin–2–ona, indazolilo, isoindolilo, isoquinolinilo, isoxazolilo, isotiazolilo, 1,8–naftiridinilo, oxazolilo, oxaindolilo, oxadiazolilo, pirazolilo, pirrolilo, ftalazinilo, pteridinilo, purinilo, piridilo, piridazinilo, pirazinilo, pirimidinilo, quinoxalinilo, quinolinilo, quinazolinilo, 4H–quinolizinilo, tiazolilo, tiadiazolilo, tienilo, triazinilo, triazolilo y tetrazolilo, cada uno de los cuales está opcionalmente sustituido con 1 a 3 grupos R^A, donde cada R^A se selecciona de manera independiente de $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, $-CN$, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$ y $-(CH_2)_nNHC(O)R^8$. En otras realizaciones de los compuestos de las Fórmulas (I)–(IX), la Fórmula (I–A) y la Fórmula (I–B), el anillo A se selecciona de piridilo, benzo[1,3]dioxol, tienilo, benzotienilo, benzofuranilo o indolilo, cada uno de los cuales está opcionalmente sustituido con 1 a 3 grupos R^A, donde cada R^A se selecciona de manera independiente de $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, $-CN$, $-N(R^9)_2$, $-NR^9C(O)R^8$,

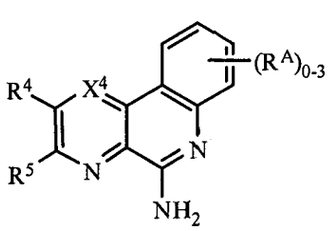
$-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$ y $-(CH_2)_nNHC(O)R^8$.

En ciertas realizaciones de los compuestos de las Fórmulas (I)–(IX), la Fórmula (I–A) y la Fórmula (I–B), el anillo A se selecciona de fenilo, tienilo y piridilo, y en otras realizaciones, dichos grupos fenilo, tienilo y piridilo están opcionalmente sustituidos con 1 a 3 grupos R^A, donde cada R^A se selecciona de modo independiente de $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, $-CN$, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$ y $-(CH_2)_nNHC(O)R^8$.

En ciertas realizaciones de los compuestos de las Fórmulas (I)–(IX), la Fórmula (I–A) y la Fórmula (I–B), el anillo A es un fenilo opcionalmente sustituido con 1 a 3 grupos R^A, donde cada R^A se selecciona de manera independiente de $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, $-CN$, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$,

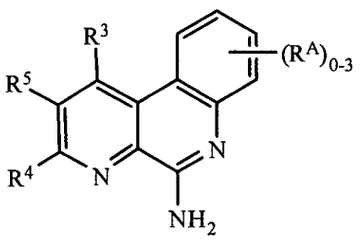
$-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$ y $-(CH_2)_nNHC(O)R^8$. En ciertas realizaciones de los compuestos de las Fórmulas (I)–(IX), la Fórmula (I–A) y la Fórmula (I–B), el anillo A es un piridilo opcionalmente sustituido con 1 a 3 grupos R^A, donde cada R^A se selecciona de manera independiente de $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, $-CN$, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$ y $-(CH_2)_nNHC(O)R^8$.

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, sus solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), los derivados de N–óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezclas de sus isómeros tienen la estructura de la Fórmula (X):



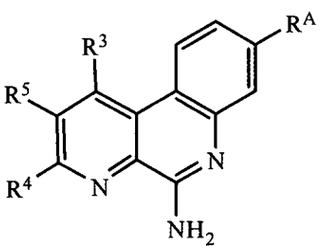
Fórmula (X).

En ciertas realizaciones, los compuestos de la Fórmula (X), sus sales aceptables para uso farmacéutico, sus solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), los derivados de N–óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezclas de sus isómeros tienen la estructura de la Fórmula (X–A):



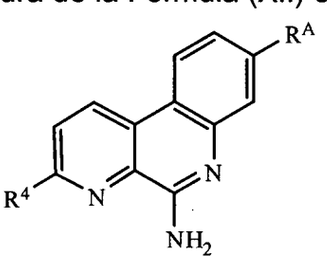
Fórmula (X–A).

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, sus solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), los derivados de N–óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezclas de sus isómeros tienen la estructura de la Fórmula (XI):

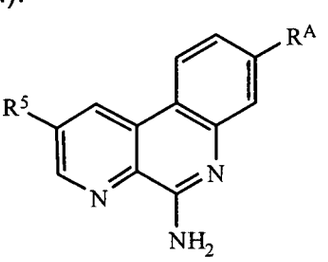


Fórmula (XI).

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, sus solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), los derivados de N–óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezclas de sus isómeros tienen la estructura de la Fórmula (XII) o la Fórmula (XIII):



Fórmula (XII)



Fórmula (XIII).

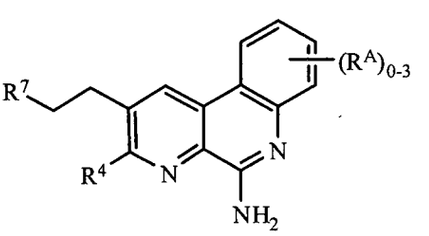
En ciertas realizaciones de los compuestos de las Fórmulas (I), (I–A), (I–B)

y (II)–(XIII), R^4 y R^5, cuando se presentan, se seleccionan de manera independiente de H, halógeno, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-SR^7$, $-(CH_2)_nOR^7$, $-(CH_2)_nR^7$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, –alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8, y heterocicloalquilo C_3–C_8, donde los grupos alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6, cicloalquilo C_3–C_8, o heterocicloalquilo C_3–C_8 de R^4 y R^5 están, cada uno, opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de modo independiente de halógeno, –CN, =O, $-NO_2$, $-R^7$, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-C(O)N(R^9)_2$, $-Si(R^8)_3$, $-S(O)_2R^8$, $S(O)R^8$, $-S(O)_2N(R^9)_2$ y $-NR^9S(O)_2R^8$, y donde los grupos arilo y heteoarilo de R^4 y R^5 están, cada uno, opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente de halógeno, –CN, $-R^7$, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-C(O)N(R^9)_2$, $-Si(R^8)_3$, $-S(O)_2R^8$, $-S(O)R^8$, $-S(O)_2N(R^9)_2$, y $-NR^9S(O)_2R^8$. En otras realizaciones, R^3 y R^4, o R^4 y R^5, o R^5 y R^6, cuando están presentes en átomos anulares adyacentes, pueden estar opcionalmente ligados entre si para formar un anillo de 5-6 miembros, donde el anillo de 5-6 miembros está opcionalmente sustituido con R^7.

En ciertas realizaciones de los compuestos de Fórmulas (I), (I-A), (I-B) y (II)–(XIII), cada L se selecciona de manera independiente de un enlace, $-(O(CH_2)_m)_t-$, alquilo C_1–C_6, alquenileno C_2–C_6 y alquinileno C_2–C_6, donde los alquilo C_1–C_6, alquenileno C_2–C_6 y alquinileno C_2–C_6 de L están, cada uno, opcionalmente sustituidos con 1 a 4 sustituyentes seleccionados independientemente de halógeno, $-R^8$, $-OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, y $-OP(O)(OR^{10})_2$.

En ciertas realizaciones de los compuestos de las Fórmulas (I), (I–A), (I–B) y (II)–(XIII), R^4 y R^5, cuando se presentan, se seleccionan de modo independiente de H, halógeno, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-SR^7$, $-(CH_2)_nOR^7$, $-(CH_2)_nR^7$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8, y heterocicloalquilo C_3–C_8, donde los grupos alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6, cicloalquilo C_3–C_8, heterocicloalquilo C_3–C_8, arilo y heteroarilo de R^4 y R^5 están, cada uno, opcionalmente sustituidos con 1 a 3 R^7.

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, sus solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), los derivados de N–óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezclas de sus isómeros tienen la estructura de la Fórmula (XIV):



Fórmula (XIV).

En ciertas realizaciones de los compuestos de las Fórmulas (I), (I–A), (I–B) y (II)–(XIV), R^7 se selecciona de H, alquilo C_1–C_6, cicloalquilo C_3–C_8, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6, y heterocicloalquilo C_3–C_8, donde los grupos alquilo C_1–C_6, cicloalquilo C_3–C_8, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6, y heterocicloalquilo C_3–C_8 de R^7 están, cada uno, opcionalmente sustituidos con 1 a 3 grupos R^{13}, y cada R^{13} se selecciona de

manera independiente de halógeno, –CN, =O, $-LR^9$, $-LOR^9$, $-OLR^9$, $-LR^{10}$, $-LOR^{10}$, $-OLR^{10}$, $-LR^8$, $-LOR^8$, $-OLR^8$, $-LSR^8$, $-LSR^{10}$, $-LC(O)R^8$, $-OLC(O)R^8$, $-LC(O)OR^8$, $-LC(O)R^{10}$, $-LOC(O)OR^8$, $-LC(O)NR^9R^{11}$, $-LC(O)NR^9R^8$, $-LN(R^9)_2$, $-LNR^9R^8$,$-LNR^9R^{10}$, $-LC(O)N(R^9)_2$, $-LS(O)_2R^8$, $-LS(O)R^8$, $-LC(O)NR^8OH$, $-LNR^9C(O)R^8$, $-LNR^9C(O)OR^8$, $-LC(=N-OR^8)R^8$, $-LC(=NH)-NHOR^8$, $-NHC(=NH)NH_2$, $-LS(O)_2N(R^9)_2$, $-OLS(O)_2N(R^9)_2$, $-LNR^9S(O)_2R^8$, $-LC(O)NR^9LN(R^9)_2$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$ y $-OLP(O)(OR^{10})_2$.

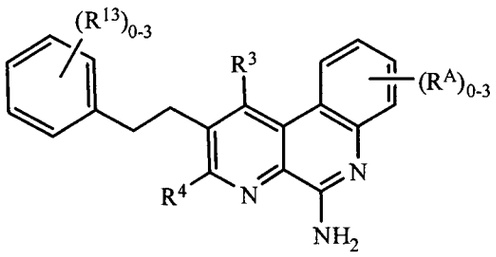
En ciertas realizaciones de los compuestos de las Fórmulas (I), (I–A), (I–B) y (II)–(XIV), R^7 es un grupo arilo o heteroarilo opcionalmente sustituido con 1 a 3 grupos R^{13}, y cada R^{13} se selecciona de modo independiente de halógeno, –CN, $-LR^9$, $-LOR^9$, $-OLR^9$, $-LR^{10}$, $-LOR^{10}$, $-OLR^{10}$, $-LR^8$, $-LOR^8$, $-OLR^8$, $-LSR^8$, $-LSR^{10}$, $-LC(O)R^8$, $-OLC(O)R^8$, $-LC(O)OR^8$, $-LC(O)R^{10}$, $-LOC(O)OR^8$, $-LC(O)NR^9R^{11}$, $-LC(O)NR^9R^8$, $-LN(R^9)_2$, $-LNR^9R^8$, $-LNR^9R^{10}$, $-LC(O)N(R^9)_2$, $-LS(O)_2R^8$, $-LS(O)R^8$, $-LC(O)NR^8OH$, $-LNR^9C(O)R^8$, $-LNR^9C(O)OR^8$, $-LC(=N-OR^8)R^8$, $-LC(=NH)-NHOR^8$, $-NHC(=NH)NH_2$, $-LS(O)_2N(R^9)_2$, $-OLS(O)_2N(R^9)_2$, $-LNR^9S(O)_2R^8$, $-LC(O)NR^9LN(R^9)_2$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$ y $-OLP(O)(OR^{10})_2$.

En ciertas realizaciones de los compuestos de las Fórmulas (I), (I–A), (I–B) y (II)–(XIV), R^7 se selecciona de H, alquilo C_1–C_6, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8, y los grupos alquilo C_1–C_6, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8, de modo independiente, están opcionalmente sustituidos con 1–3 grupos R^{13}, y cada R^{13} se selecciona de manera independiente de halógeno, =O, haloalquilo C_1–C_6, LR^8, LR^9, OLR^8 y $-LOR^8$.

En ciertas realizaciones de los compuestos de las Fórmulas (I), (I–A), (I–B) y (II)–(XIV), R^7 es un grupo arilo o heteroarilo opcionalmente sustituido con 1–3 grupos R^{13}, y cada R^{13} se selecciona de manera independiente de halógeno,

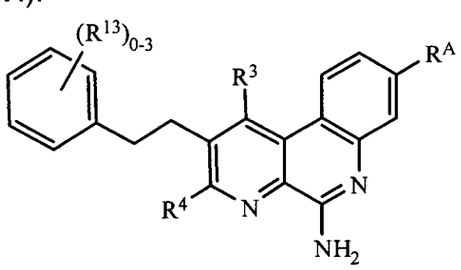
haloalquilo C_1–C_6, LR^8, LR^9, OLR^8 y $–LOR^8$.

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, sus solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), los derivados de N–óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezclas de sus isómeros tienen la estructura de la Fórmula (XV):



Fórmula (XV).

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, sus solvatos aceptables para uso farmacéutico (por ejemplo, hidratos), los derivados de N–óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezclas de sus isómeros tienen la estructura de la Fórmula (XVI):



Fórmula (XVI).

En determinados compuestos de Fórmula (XV) o (XVI), R^4, R^A y R^{13} se seleccionan de manera independiente de H, $–CH_3$, $–CH_2CH_3$, $–CF_3$, $–CH_2OH$, $–OCH_3$, $–COOCH_3$, $–COOCH_2CH_3$, F, Cl, Br, $–CH_2OCH_3$, $CH_2OCH_2CH_3$, $–N(CH_3)_2$, $–((O(CH_2)_2)_{2\text{-}4}OH$, $–O(CH_2)_{2\text{-}4}–OH$, $–O(CH_2)_{2\text{-}4}–(PO_3H_2)$, $–O(CH_2)_{2\text{-}4}–COOH$, $–O(CH_2)_{2\text{-}4}–CH(CH_3)_2$, alquilo C_2–C_6 sustituido con 1-3 sustituyentes seleccionados de –OH, $–CH_3$, ciclopropilo, $–O(CH_2)_{2\text{-}4}–COOH$, $–O(CH_2)_{2\text{-}4}(PO_3H_2)$,

–COOH, $COOCH_3$, y $-COOCH_2CH_3$. En algunas realizaciones de tales compuestos, R^4 es H. En algunos de estos compuestos, el anillo fenilo del grupo fenetilo tiene uno a tres grupos R^{13}. Opcionalmente, R^A es H o $-CH_3$. En ciertas realizaciones, estos compuestos poseen dos grupos R^{13} presentes, y estos grupos R^{13} están seleccionados del grupo formado por $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH_2OH$, $-OCH_3$, $-COOCH_3$, $-COOCH_2CH_3$, F, Cl, Br, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-N(CH_3)_2$, $-((O(CH_2)_2)_{2-4}OH$, $-O(CH_2)_{2-4}-OH$, $-O(CH_2)_{2-4}-(PO_3H_2)$, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}-CH(CH_3)_2$, alquilo C_2–C_6 sustituido con 1-3 sustituyentes seleccionados de –OH, $-CH_3$, ciclopropilo, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}(PO_3H_2)$, –COOH, $COOCH_3$, y $-COOCH_2CH_3$.

En ciertas realizaciones de los compuestos de Fórmula XIII, XIV, XV o XVI, el compuesto se selecciona de: 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol; 2–(4–metoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato de etilo; 2–(4–(dimetilamino)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina, y 2–(4–metoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina. Cada uno de estos compuestos comprende de manera individual una realización preferida de los compuestos, composiciones, y métodos descriptos en la presente.

En ciertas realizaciones, los compuestos de la Fórmula (I) que se describen en la presente solicitud se combinan con un antígeno, y opcionalmente, un portador, un excipiente o coadyuvante farmacéuticamente aceptable, a fin de proporcionar una composición inmunógena. En ciertas realizaciones, los compuestos de la Fórmula (XVI) como se describen en esta solicitud se combinan con un antígeno, y opcionalmente, un portador, excipiente o coadyuvante farmacéuticamente aceptable, a fin de proporcionar una composición inmunógena. En otras realizaciones, dicha composición inmunógena comprende

un compuesto de la Fórmula (I) y un antígeno, donde el antígeno incluye, sin limitación, un antígeno bacteriano, un antígeno viral, un antígeno fúngico, un antígeno tumoral, o un antígeno asociado con STD (enfermedad de transmisión sexual, por sus siglas en inglés), la enfermedad de Alzheimer, trastornos respiratorios, trastornos autoinmunitarios tales como, solo a modo de ejemplo, artritis reumatoide o lupus; trastornos pediátricos y obesidad; y donde la cantidad del compuesto es una cantidad eficaz para mejorar una respuesta inmunitaria al antígeno en un sujeto al cual es administrada la composición. En otras realizaciones, dicha composición inmunógena comprende un compuesto de la Fórmula (XVI) y un antígeno, donde el antígeno incluye, sin limitación, un antígeno bacteriano, un antígeno viral, un antígeno fúngico, un antígeno tumoral, o un antígeno asociado con STD, la enfermedad de Alzheimer, trastornos respiratorios, trastornos autoinmunitarios tales como, solo a modo de ejemplo, artritis reumatoide o lupus; trastornos pediátricos y obesidad; y donde la cantidad del compuesto es una cantidad eficaz para mejorar una respuesta inmunitaria al antígeno en un sujeto al cual es administrada la composición. Los antígenos adecuados para el uso en dichas composiciones inmunógenas se describen en la presente solicitud.

En ciertas realizaciones, dichas composiciones inmunógenas incluyen un antígeno bacteriano de una cepa de *Neisseria meningitides*, tal como el serogrupo A, C, W135, Y y/o B. Los antígenos específicos para el uso en estas composiciones son los descriptos en la presente solicitud. En otras realizaciones, dichas composiciones inmunógenas y otras proporcionadas en esta solicitud se usan como vacunas; su uso en el tratamiento de trastornos asociados con el antígeno incluido en la composición se describe en esta solicitud.

En ciertas realizaciones de los compuestos de las Fórmulas (I), (I–A), (I–B) y (II)–(XVI), cada R^{13} se selecciona de manera independiente de LR^{10}, LOR^{10},

LR^8, $-LOR^8$, $-LSR^8$, LSR^{10}, $-LC(O)OR^8$, $-LN(R^9)_2$, $-LC(O)N(R^9)_2$, $-LS(O)_2R^8$, $-LS(O)R^8$, $-LP(O)(OR^8)_2$, $-OLP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$ y $-OLP(O)(OR^{10})_2$.

En ciertas realizaciones de los compuestos de Fórmulas (I), (I-A), (I-B) y (II)–(XVI), cada L se selecciona de manera independiente de un enlace, $-(O(CH_2)_m)_t-$, alquilo C_1–C_6, alquenileno C_2–C_6 y alquinileno C_2–C_6, donde los alquilo C_1–C_6, alquenileno C_2–C_6 y alquinileno C_2–C_6 de L están, cada uno, opcionalmente sustituidos con 1 a 4 sustituyentes seleccionados independientemente de halógeno, $-R^8$, $-OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, y $-OP(O)(OR^{10})_2$.

En ciertas realizaciones de los compuestos de las Fórmulas (I), (I–A), (I–B) y (II)–(XVI), R^1 y R^2 son, independientemente, H.

En ciertas realizaciones de los compuestos de las Fórmulas (I), (I–A), (I–B) y (II)–(XVI), R^3 y R^6, cuando se presentan, se seleccionan de manera independiente de H, halógeno, alquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8 y alcoxi C_1–C_6.

En ciertas realizaciones de los compuestos de las Fórmulas (I), (I–A), (I–B) y (II)–(XVI), R^{10} es un arilo o un heteroarilo, donde los grupos arilo y heteroarilo están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de halógeno, $-R^8$, $-OR^8$ y $-N(R^9)_2$. En otras realizaciones de los compuestos de las Fórmulas (I), (I–A), (I–B) y (II)–(XVI), R^{10} es fenilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de halógeno, $-R^8$, $-OR^8$ y $-N(R^9)_2$.

En ciertas realizaciones de los compuestos de las Fórmulas (I), (I–A), (I–B) y (II)–(XIII), R^8 se selecciona de H, alquilo C_1–C_6 y haloalquilo C_1–C_6.

En ciertas realizaciones, el compuesto de la Fórmula (I) es 3–cloro–2–metilbenzo[f][1,7]naftiridin–5–amina; 2–metilbenzo[f][1,7]naftiridin–5–amina; pirimido[4,5–c]quinolin–5–amina; 2–(etoximetil)benzo[f][1,7]naftiridin–5–amina; pirimido[4,5–c]quinolina–3,5–diamina; 3–(metiltio)pirimido[4,5–c]quinolin–5–

amina; (E)–2–(2–ciclopropilvinil)benzo[f][1,7]naftiridin–5–amina; (E)–2–(pent–1–enil)benzo[f][1,7]naftiridin–5–amina; 4–(5–aminobenzo[f][1,7]naftiridin–2–il)–2–metilbut–3–in–2–ol; 2–pentilbenzo[f][1,7]naftiridin–5–amina; (E)–2–(prop–1–enil)benzo[f][1,7]naftiridin–5–amina; (E)–2–(3–fenilprop–1–enil)benzo[f][1,7]naftiridin–5–amina; 2–(2–ciclopropiletil)benzo[f][1,7]naftiridin–5–amina; 4–(5–aminobenzo[f][1,7]naftiridin–2–il)–2–metilbutan–2–ol; 2–propilbenzo[f][1,7]naftiridin–5–amina; 2–(3–fenilpropil)benzo[f][1,7]naftiridin–5–amina; 2–etilbenzo[f][1,7]naftiridin–5–amina; 2–(2–metilprop–1–enil)benzo[f][1,7]naftiridin–5–amina; 2–isobutilbenzo[f][1,7]naftiridin–5–amina; (E)–2–(2,4–difluorestiril)benzo[f][1,7]naftiridin–5–amina; (E)–2–(hex–1–enil)benzo[f][1,7]naftiridin–5–amina; (E)–2–(2–ciclohexilvinil)benzo[f][1,7]naftiridin–5–amina; E)–2–(3–(trifluormetil)estiril)benzo[f][1,7]naftiridin–5–amina; (E)–2–(3–metoxiestiril)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–vinilbenzo[f][1,7]naftiridin–5–amina; (E)–8–metil–2–estirilbenzo[f][1,7]naftiridin–5–amina; 2–(2–ciclohexiletil)benzo[f][1,7]naftiridin–5–amina; 2–fluorbenzo[f][1,7]naftiridin–5–amina; 2–(3–(trifluormetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,4–difluorfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(3–metoxifenetil)benzo[f][1,7]naftiridin–5–amina; 2–hexilbenzo[f][1,7]naftiridin–5–amina; 2–etil–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–fenetilbenzo[f][1,7]naftiridin–5–amina; metil 5–aminobenzo[f][1,7]naftiridina–3–carboxilato; 5–amino–N–metilbenzo[f][1,7]naftiridina–3–carboxamida; (5–aminobenzo[f][1,7]naftiridin–3–il)metanol; 8–fenilbenzo[f][1,7]naftiridin–5–amina; 3–(etoximetil)benzo[f][1,7]naftiridin–5–amina; benzo[f][1,7]naftiridina–3,5–diamina; benzo[f][1,7]naftiridin–5–amina; metil 5–aminobenzo[f][1,7]naftiridina–8–carboxilato; ácido 5–aminobenzo[f][1,7]naftiridina–8–carboxílico; etil 5–aminobenzo[f][1,7]naftiridina–8–carboxilato; (5–aminobenzo[f][1,7]naftiridin–8–

il)metanol; ácido 5–aminobenzo[f][1,7]naftiridina–3–carboxílico; 5–aminobenzo[f][1,7]naftiridina–3–carbaldehído; 2–(o–toliletinil)benzo[f][1,7]naftiridin–5–amina; 2–(m–toliletinil)benzo[f][1,7]naftiridin–5–amina; 2–(p–toliletinil)benzo[f][1,7]naftiridin–5–amina; 2–(2–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(3–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 3–cloro–2–(etoximetil)benzo[f][1,7]naftiridin–5–amina; pirazino[2,3–c]quinolin–5–amina; 9–clorobenzo[f][1,7]naftiridin–5–amina; 8–clorobenzo[f][1,7]naftiridin–5–amina; 9–metilbenzo[f][1,7]naftiridin–5–amina; 10–metilbenzo[f][1,7]naftiridin–5–amina; etil 5–aminobenzo[f][1,7]naftiridina–9–carboxilato; ácido 5–aminobenzo[f][1,7]naftiridina–9–carboxílico; 8–metoxibenzo[f][1,7]naftiridin–5–amina; 7–fluorbenzo[f][1,7]naftiridin–5–amina; 8–(metilsulfonil)benzo[f][1,7]naftiridin–5–amina; 8–(trifluormetil)benzo[f][1,7]naftiridin–5–amina; 8–fluorbenzo[f][1,7]naftiridin–5–amina; 3–metoxibenzo[f][1,7]naftiridin–5–amina; 3–butoxibenzo[f][1,7]naftiridin–5–amina; 3–(benciloxi)benzo[f][1,7]naftiridin–5–amina; 3–metilbenzo[f][1,7]naftiridin–5–amina; 3–clorobenzo[f][1,7]naftiridin–5–amina; N^3,N^3–dimetilbenzo[f][1,7]naftiridina–3,5–diamina; N^3–butilbenzo[f][1,7]naftiridina–3,5–diamina; 3–vinilbenzo[f][1,7]naftiridin–5–amina; 3–etilbenzo[f][1,7]naftiridin–5–amina; 3–fluorbenzo[f][1,7]naftiridin–5–amina; 2–(trifluormetil)benzo[f][1,7]naftiridin–5–amina; 2–metoxibenzo[f][1,7]naftiridin–5–amina; 2–(benciloxi)benzo[f][1,7]naftiridin–5–amina; 2–vinilbenzo[f][1,7]naftiridin–5–amina; 2–fenilbenzo[f][1,7]naftiridin–5–amina; (E)–2–estirilbenzo[f][1,7]naftiridin–5–amina; 2–fenetilbenzo[f][1,7]naftiridin–5–amina; (E)–2–(3–metoxiprop–1–enil)benzo[f][1,7]naftiridin–5–amina; 2–(3–metoxipropil)benzo[f][1,7]naftiridin–5–amina; 2–(prop–1–en–2–

il)benzo[f][1,7]naftiridin–5–amina; 2–isopropilbenzo[f][1,7]naftiridin–5–amina; 1–metilbenzo[f][1,7]naftiridin–5–amina; benzo[c][1,8]naftiridin–6–amina; pirido[3,2–f][1,7]naftiridin–6–amina; tieno[2,3–c]quinolin–4–amina; 8–metil–2–(naftalen–2–iletinil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2–(naftalen–1–il)etil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2–(naftalen–2–il)etil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(naftalen–1–iletinil)benzo[f][1,7]naftiridin–5–amina; ácido 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoico; ácido 3–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoico; 2–(3–clorofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–clorofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; (3–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)metanol; 2–(4–clorofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–(trifluormetil)fenantridin–6–amina; benzo[c][2,7]naftiridin–5–amina; 2–(trifluormetil)benzo[f][1,7]naftiridin–5–amina; 2–ter–butoxibenzo[f][1,7]naftiridin–5–amina; 5–aminobenzo[f][1,7]naftiridin–2–ol; 2–((4–butilfenil)etinil)benzo[f][1,7]naftiridin–5–amina; 2–(4–butilfenetil)benzo[f][1,7]naftiridin–5–amina; 1–bencil–5–cloro–7–(trifluormetil)–1,2–dihidropirido[3,4–b]pirazin–3(4H)–ona; 2–(2–(6–metoxinaftalen–2–il)etil)benzo[f][1,7]naftiridin–5–amina; 2–(4–butilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–propilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(trifluormetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,5–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–propilfenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2,4,5–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,5–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–isopropilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–heptilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; (Z)–2–(2–(bifenil–4–il)vinil)–8–

metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–isobutoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–((2–metoxietoxi)metoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(2–fenoxietoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(ter–butildimetilsililoxi)etoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–butoxi–2–metilfenetil)–N–butil–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(4–fenilbutoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(aliloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(3–fenilpropoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(heptan–4–iloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(4–metilpent–3–eniloxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–ciclohexiletoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–isopropoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(3,3–dimetilbutoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(ter–butildimetilsililoxi)etoxi)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)–2–(4–(dimetilamino)fenetil)benzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)–2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; dietil 3–(2–(4–(2–(2–hidroxietoxi)etoxi)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–ilamino)propilfosfonato; (E)–N–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)vinil)fenil)acetamida; N–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)acetamida; N–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)fenil)acetamida; N–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)–4–metilbencenosulfonamida; 3–metil–9–p–tolil–9,10–dihidrobenzo[f]furo[2,3–b][1,7]naftiridin–6–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzonitrilo; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–aminoetil)–3–metilbenzamida; ácido 2–(4–(2–(5–amino–3–cloro–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–

metilbenzamido)acético; ácido (S)–2–(4–(2–(5–amino–3–cloro–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)–4–metilpentanoico; 4–(2–(5–amino–3–cloro–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N,3–dimetilbenzamida; 8–metil–2–(2–metil–4–(1H–tetrazol–5–il)fenetil)benzo[f][1,7]naftiridin–5–amina; metil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)–4–metilpentanoato; metil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)acetato; ácido 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)–4–metilpentanoico; ácido 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)acético; 6–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)hexan–1–ol; ácido 7–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)heptanoico; 11–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)undecan–1–ol; 2–fenetilbenzo[f][1,7]naftiridin–5–amina; etil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)acetato; ácido 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)acético; ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propanoico; ácido 6–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)hexanoico; 8–metil–2–(2–metil–4–(metiltio)fenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(metilsulfonil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(hexiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–fenetoxifenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–ciclobutoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(pentiloxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(4–metilpentiloxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 8–bromo–3–metoxibenzo[f][1,7]naftiridin–5–amina; 2–((ter–butildimetilsilil)etinil)benzo[f][1,7]naftiridin–5–amina; 2–((2–

fluorfenil)etinil)benzo[f][1,7]naftiridin–5–amina; 2–((3–fluorfenil)etinil)benzo[f][1,7]naftiridin–5–amina; 2–((4–fluorfenil)etinil)benzo[f][1,7]naftiridin–5–amina; 2–(tiofen–3–iletinil)benzo[f][1,7]naftiridin–5–amina; 2–etinilbenzo[f][1,7]naftiridin–5–amina; 2–(2–fluorfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(3–fluorfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–fluorfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2–(tiofen–3–il)etil)benzo[f][1,7]naftiridin–5–amina; etil 5–aminobenzo[f][1,7]naftiridina–2–carboxilato; etil 5–amino–8–metilbenzo[f][1,7]naftiridina–2–carboxilato; (5–aminobenzo[f][1,7]naftiridin–2–il)metanol; 2–(3,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 1–cloro–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–1–(3–fenilpropil)benzo[f][1,7]naftiridin–5–amina; (Z)–2–(2–(benzo[d][1,3]dioxol–5–il)vinil)–8–metilbenzo[f][1,7]naftiridin–5–amina; (Z)–2–(4–metoxi–2–metilestiril)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(3,4–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(3,5–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(1–fenilvinil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–fenilbutil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(1–feniletil)benzo[f][1,7]naftiridin–5–amina; 2–(2–(benzofuran–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; (Z)–2–(2–etoxivinil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–etoxietil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(clorometil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2–nitroetil)benzo[f][1,7]naftiridin–5–amina; dietil 2–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)metil)malonato; 2–(isopropilsulfonil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–((metoximetoxi)metil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–((metilamino)metil)benzo[f][1,7]naftiridin–5–amina; ter–butil 5–amino–8–metilbenzo[f][1,7]naftiridin–2–ilcarbamato; 8–metil–2–

((fenilamino)metil)benzo[f][1,7]naftiridin–5–amina; 2–(aminometil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(pirrolidin–1–ilmetil)benzo[f][1,7]naftiridin–5–amina; N^2–(2,4–dimetoxibencil)–8–metilbenzo[f][1,7]naftiridina–2,5–diamina; N^2,N^2,8–trimetilbenzo[f][1,7]naftiridina–2,5–diamina; N^2,8–dimetilbenzo[f][1,7]naftiridina–2,5–diamina; 8–metil–2–(pirrolidin–1–il)benzo[f][1,7]naftiridin–5–amina; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–feniletanol; 2–(2–aminoetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–hidrazinil–8–metilbenzo[f][1,7]naftiridin–5–amina; 1–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–2–metilpropan–2–ol; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–(4–metoxifenil)etanol; 2–(bifenil–2–il)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(2,6–dimetilpiridin–3–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(5–metoxipiridin–2–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propanoico; 5–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–4–metilpiridin–2(1H)–ona; 6–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)piridin–3–ol; 3–metildibenzo[b,f][1,7]naftiridin–6–amina; 8–metil–2–(4–(trifluormetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2–(2,3–dihidro–1H–inden–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(2,3–dihidro–1H–inden–5–il)etil)benzo[f][1,7]naftiridin–5–amina; ácido (E)–3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)acrílico; (E)–etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)acrilato; N^3,N^5–dibutilbenzo[f][1,7]naftiridina–3,5–diamina; 8–(prop–1–en–2–il)benzo[f][1,7]naftiridin–5–amina; 5–aminobenzo[f][1,7]naftiridina–8–carbonitrilo; (E)–8–(3–metilbut–1–enil)benzo[f][1,7]naftiridin–5–amina; 8–(2–metilprop–1–enil)benzo[f][1,7]naftiridin–5–amina; (E)–8–(pent–1–enil)benzo[f][1,7]naftiridin–5–amina; (E)–8–estirilbenzo[f][1,7]naftiridin–5–amina; (E)–8–(2–ciclopropilvinil)–2–fenetilbenzo[f][1,7]naftiridin–5–amina; 8–pentilbenzo[f][1,7]naftiridin–5–amina; (E)–

8–(2–ciclopropilvinil)benzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)–2–fenetilbenzo[f][1,7]naftiridin–5–amina; pirido[1,2–c][1,7]naftiridin–6–amina; 9–fenetilpirido[1,2–c][1,7]naftiridin–6–amina; metil 5–amino–2–(4–metoxifenetil)benzo[f][1,7]naftiridina–8–carboxilato; 8–nitrobenzo[f][1,7]naftiridin–5–amina; 3–cloro–8–metilbenzo[f][1,7]naftiridin–5–amina; metil 5–amino–3–clorobenzo[f][1,7]naftiridina–8–carboxilato; metil 5–amino–3–fluorbenzo[f][1,7]naftiridina–8–carboxilato; 3–cloro–8–nitrobenzo[f][1,7]naftiridin–5–amina; (5–amino–3–clorobenzo[f][1,7]naftiridin–8–il)metanol; (5–amino–2–fenetilbenzo[f][1,7]naftiridin–8–il)metanol; 4–(2–(5–amino–8–fluorbenzo[f][1,7]naftiridin–2–il)etil)benzaldehído; 2–(4–(2–(5–amino–8–fluorbenzo[f][1,7]naftiridin–2–il)etil)bencilamino)etanol; 3–(4–(2–(5–amino–8–fluorbenzo[f][1,7]naftiridin–2–il)etil)bencilamino)propan–1–ol; 8–fluor–2–(4–((2–metoxietilamino)metil)fenetil)benzo[f][1,7]naftiridin–5–amina; 8–((ter–butildimetilsililoxi)metil)–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–5–amina; (5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)metanol; 3–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)fenol; 2–(2–metoxifenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–etilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–etilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(dimetilamino)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(piperidin–1–il)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–ter–butilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(piperidin–1–il)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–metoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(3,5–dimetoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2–(trifluormetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2–(1–metil–1H–imidazol–5–il)etil)benzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–

metilbenzo[f][1,7]naftiridin–2–il)etil)–N–hidroxibencimidamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzonitrilo; 8–metil–2–(4–(1–morfolinoetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–aminofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)guanidina; 8–metil–2–(4–(1–(fenetilamino)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)acetonitrilo; 2–(4–(piperidin–1–ilmetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 1–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)bencil)piperidin–4–ol; 2–(4–(aminometil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–((etilamino)metil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–aminopropan–2–il)fenetil)benzo[f][1,7]naftiridin–5–amina; ácido 1–(1–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidina–3–carboxílico; 8–metil–2–(4–(1–(fenilamino)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–etil–8–metilbenzo[f][1,7]naftiridin–5–amina; (5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)metanol; 8–metil–2–propilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(1H–indol–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–etoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–fenoxifenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,4–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–metoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol; 2–(2–(2,3–dihidrobenzofuran–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etanol; 3–metil–9–fenil–9,10–dihidrobenzo[f]furo[2,3–b][1,7]naftiridin–6–amina; 8–metilbenzo[f][1,7]naftiridina–2,5–diamina; 1–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)propan–2–ol; 2–(5–

amino–8–metilbenzo[f][1,7]naftiridin–2–il)acetonitrilo; N–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)acetamida; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–(2,4–dimetilfenil)etanol; 2–(2–(6–metoxi–4–metilpiridin–3–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)butan–1–ol; metil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propanoato; 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propan–1–ol; 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)–2–metilbutan–2–ol; 2–(4–(aminometil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; (E)–etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)acrilato; etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propanoato; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbencil)propano–1,3–diol; ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propanoico; 5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridina–8–carbaldehído; etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoato; 8–metil–2–(4–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propan–2–ol; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)metanol; etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato; ácido 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoico; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)metanol; 8–metil–2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol; 8–metil–2–(4–propoxifenetil)benzo[f][1,7]naftiridin–5–amina; (E)–etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)acrilato; ácido (E)–3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)acrílico; etil 3–(5–amino–2–(4–

metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propanoato; ácido 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propanoico; 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propan–1–ol; (5–aminobenzo[f][1,7]naftiridin–8–il)metanol; 5–aminobenzo[f][1,7]naftiridin–8–ol; 5–aminobenzo[f][1,7]naftiridina–8–carbaldehído; 1–(5–aminobenzo[f][1,7]naftiridin–8–il)etanol; 1–(5–aminobenzo[f][1,7]naftiridin–8–il)etanona; 8–isopropilbenzo[f][1,7]naftiridin–5–amina; 8–vinilbenzo[f][1,7]naftiridin–5–amina; 8–etilbenzo[f][1,7]naftiridin–5–amina; 8–(metoximetil)benzo[f][1,7]naftiridin–5–amina; (5–amino–2–fenetilbenzo[f][1,7]naftiridin–8–il)metanol; (5–amino–2–(4–metoxifenetil)benzo[f][1,7]naftiridin–8–il)metanol; benzo[f][1,7]naftiridina–5,8–diamina; 8–(aminometil)benzo[f][1,7]naftiridin–5–amina; 3–fluor–8–metilbenzo[f][1,7]naftiridin–5–amina; (5–amino–3–fluorbenzo[f][1,7]naftiridin–8–il)metanol; 3–clorobenzo[f][1,7]naftiridina–5,8–diamina; 3–fluorbenzo[f][1,7]naftiridina–5,8–diamina; 8–isobutilbenzo[f][1,7]naftiridin–5–amina; (E)–8–(prop–1–enil)benzo[f][1,7]naftiridin–5–amina; 8–propilbenzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)benzo[f][1,7]naftiridin–5–amina; 8–fenetilbenzo[f][1,7]naftiridin–5–amina; (5–amino–2–(4–bromofenetil)benzo[f][1,7]naftiridin–8–il)metanol; 2–(4–metoxi–2–metilfenetil)–8–pentilbenzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–5–amina; (5–amino–2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–8–il)metanol; (5–amino–2–(4–propoxifenetil)benzo[f][1,7]naftiridin–8–il)metanol; (2–(2–(1H–indol–5–il)etil)–5–aminobenzo[f][1,7]naftiridin–8–il)metanol; N–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)acetamida; metil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N,3–dimetilbenzamida; N–(2–acetamidoetil)–4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamida; 4–(2–

(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N,3–dimetilbenzamida; 2–(4–metoxifenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N,N,3–trimetilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–hidroxietil)–3–metilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–3–metilbenzamida; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(pirrolidin–1–il)metanona; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dietilamino)etil)–3–metilbenzamida; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(4–etilpiperazin–1–il)metanona; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(piperazin–1–il)metanona; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metil–N–(2–(pirrolidin–1–il)etil)benzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–aminoetil)–3–metilbenzamida; 4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N,3–dimetilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N–metilbenzamida; 2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol; 2–(4–butoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(bifenil–4–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–((1,3–dihidroisobenzofuran–1–il)metil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(2–metilaliloxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(isopentiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil propil carbonato; etil 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)pentanoato; 2–(4–(ciclopentiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(ciclobutilmetoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(2–

morfolinoetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)–1–feniletanona; ácido 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)pentanoico; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)etanol; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)–N,N–dimetilacetamida; 8–metil–2–(2–metil–4–(2–morfolinoetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etanol; dietil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propilfosfonato; ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propilfosfónico; 2–(4–butoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol; 2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol; etil 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)pentanoato; ácido 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)pentanoico; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil etil carbonato; metil 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)butanoato; ácido 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)butanoico; ácido 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)butanoico; 2–(4–(isopentiloxi)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil hexil carbonato; 2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina; (5–amino–2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–8–il)metanol; dietil 3–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)propilfosfonato; dietil 3–(2–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etoxi)propilfosfonato; 4–(2–(5–amino–8–

metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil dimetilsulfamato; (5–amino–2–(4–(dimetilamino)fenetil)benzo[f][1,7]naftiridin–8–il)metanol; 2–(4–(dimetilamino)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol; 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona; 2–(4–((dimetilamino)metil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(1–(dimetilamino)etil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona oxima; 8–metil–2–(4–((metilamino)metil)fenetil)benzo[f][1,7]naftiridin–5–amina; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)bencilamino)etanol; 8–metil–2–(4–(pirrolidin–1–ilmetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(3,4–dimetoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)etanol; 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanol; 8–metil–2–(4–(oxazol–5–il)fenetil)benzo[f][1,7]naftiridin–5–amina; 3–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propanonitrilo; (2R)–2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propan–1–ol; 8–metil–2–(4–(1–(piperazin–1–il)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; ((2S)–1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidin–2–il)metanol; N^1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^2,N^2–dimetiletano–1,2–diamina; ácido 3–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propanoico; 8–metil–2–(4–(1–(4–metilpiperazin–1–il)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; N^2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^1,N^1–dimetilpropano–1,2–diamina; 8–metil–2–(4–(1–(2–(piridin–4–il)etilamino)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; N^1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^2,N^2–dietiletano–1,2–diamina; 2–(4–

(dimetilamino)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; ácido 1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidina–3–carboxílico; 4–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)fenol; 1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2 il)etil)fenil)etil)pirrolidin–3–ol; y 2–(4–(2–aminopropan–2–il)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

Los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, y las composiciones farmacéuticas que se proveen en la presente solicitud además incluyen todas las variaciones isotópicas adecuadas de dichos compuestos, y sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, y composiciones farmacéuticas. Una variación isotópica de un compuesto provisto en esta solicitud o de una de sus sales farmacéuticamente aceptables se define como aquella donde por lo menos un átomo es reemplazado por un átomo que tiene el mismo número atómico, pero una masa atómica diferente de la masa atómica hallada habitualmente en la naturaleza. Ejemplos de isótopos que pueden incorporarse en los compuestos que aquí se proveen y sus sales aceptables para uso farmacéutico incluyen, sin limitación, isótopos de hidrógeno, carbono, nitrógeno y oxígeno, tales como ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{35}S, ^{18}F, ^{36}Cl y ^{123}I. Ciertas variaciones isotópicas de los compuestos que se proveen en la presente solicitud y sus sales aceptables para uso farmacéutico, por ejemplo, aquellas en las cuales se incorpora un isótopo radiactivo tal como ^{3}H o ^{14}C, son útiles en estudios de distribución de tejido de sustrato o fármaco. En ejemplos particulares, pueden usarse isótopos ^{3}H y ^{14}C por su facilidad de preparación y detección. En otros ejemplos, la sustitución con isótopos tales como ^{2}H puede lograr ciertas ventajas terapéuticas que resultan de la mayor estabilidad metabólica, por ejemplo, la mayor semivida *in vivo* o las menores necesidades de

dosificación. Las variaciones isotópicas de los compuestos y de sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros y de composiciones farmacéuticas que aquí se provee se preparan por medio de procedimientos convencionales usando variaciones isotópicas apropiadas de reactivos adecuados.

Procesos para la elaboración de compuestos de la Fórmula (I).

Los procedimientos generales para la preparación de compuestos de la Fórmula (I) se describen en los Ejemplos que siguen. En las reacciones descriptas, los grupos funcionales reactivos, por ejemplo, grupos hidroxi, amino, imino, tio o carboxi, donde estos se desean en el producto final, pueden ser protegidos a fin de evitar su participación indeseada en las reacciones. Los grupos protectores convencionales pueden usarse de acuerdo con la práctica estándar (ver, por ejemplo, la referencia de T. W. Greene y P. G. M. Wuts, en: *Protective Groups in Organic Chemistry*, John Wiley and Sons, 1991).

En ciertas realizaciones, los compuestos de la Fórmula (I) que se describen en la presente solicitud se preparan como una sal de adición de ácido aceptable para uso farmacéutico, mediante la reacción de la forma de base libre del compuesto de la Fórmula (I) con un ácido inorgánico o un ácido orgánico farmacéuticamente aceptable. En otras realizaciones, una sal de adición de base aceptable para uso farmacéutico de los compuestos de la Fórmula (I) que aquí se describen se prepara mediante la reacción de la forma de ácido libre del compuesto de la Fórmula (I) con una base inorgánica o una base orgánica farmacéuticamente aceptable. De modo alternativo, las formas de sales de los compuestos de la Fórmula (I) que se describen en la presente solicitud se preparan empleando sales de los materiales iniciales o de los intermediarios. En ciertas realizaciones, los compuestos de la Fórmula (I) que se describen en la

presente solicitud se presentan en forma de otras sales, que incluyen, sin limitación, oxalatos y trifluoracetatos. En ciertas realizaciones, se forman hemisales de ácidos y bases, por ejemplo, sales de hemisulfato y hemicálcicas.

Dichas sales de adición de ácido farmacéuticamente aceptables de los compuestos de la Fórmula (I) incluyen, sin limitación, sales de bromhidrato, clorhidrato, sulfato, nitrato, succinato, maleato, formiato, acetato, adipato, besilato, bicarbonato/carbonato, propionato, fumarato, citrato, tartrato, lactato, benzoato, salicilato, glutamato, aspartato, p–toluensulfonato, bencenosulfonato, metanosulfonato, etanosulfonato, naftalenosulfonato (por ejemplo, 2–naftalenosulfonato), sal de hexanoato, bisulfato/sulfato, borato, camsilato, ciclamato, edisilato, esilato, gluceptato, gluconato, glucuronato, hexafluorfosfato, hibenzato, clorhidrato/cloruro, bromhidrato/bromuro, yodhidrato/yoduro, isetionato, lactato, malato, malonato, mesilato, metilsulfato, naftilato, 2–napsilato, nicotinato, orotato, oxalato, palmitato, pamoato, fosfato/hidrogenofosfato/dihidrogenofosfato, piroglutamato, sacarato, estearato, tanato, tosilato, trifluoracetato y xinofoato.

Los ácidos orgánicos o inorgánicos utilizados para la formación de ciertas sales de adición de ácido aceptables para uso farmacéutico de los compuestos de la Fórmula (I) incluyen, sin limitación, ácidos bromhídrico, clorhídrico, sulfúrico, nítrico, fosfórico, succínico, maleico, fórmico, acético, propiónico, fumárico, cítrico, tartárico, láctico, benzoico, salicílico, glutámico, aspártico, p–toluensulfónico, bencenosulfónico, metanosulfónico, etanosulfónico, naftalenosulfónico tal como 2–naftalenosulfónico, o hexanoico.

Dichas sales de adición de base aceptables para uso farmacéutico de un compuesto de la Fórmula (I) incluyen, sin limitación, sales de aluminio, arginina, benzatina, calcio, colina, dietilamina, diolamina, glicina, lisina, magnesio, meglumina, olamina, potasio, sodio, trometamina y zinc.

En ciertas realizaciones, las formas de ácido libre o de base libre de los

compuestos de la Fórmula (I) que se describen en la presente solicitud se preparan a partir de la correspondiente sal de adición de base o sal de adición de ácido, respectivamente. Por ejemplo, un compuesto de la Fórmula (I) en forma de una sal de adición de ácido se convierte en la correspondiente base libre mediante el tratamiento con una base adecuada (solo a modo de ejemplo, una solución de hidróxido de amonio, hidróxido de sodio y similares). Por ejemplo, un compuesto de la Fórmula (I) en forma de una sal de adición de base se convierte en el correspondiente ácido libre mediante el tratamiento con un ácido adecuado (solo a modo de ejemplo, ácido clorhídrico).

En ciertas realizaciones, los compuestos de la Fórmula (I) en forma no oxidada se preparan a partir de N–óxidos de compuestos de la Fórmula (I), mediante el tratamiento con un agente reductor (solo a modo de ejemplo, azufre, dióxido de azufre, trifenilfosfina, borohidruro de litio, borohidruro de sodio, tricloruro de fósforo, tribromuro, o similares) en un solvente orgánico inerte adecuado (solo a modo de ejemplo, acetonitrilo, etanol, dioxano acuoso o similares), a 0 a 80°C.

En ciertas realizaciones, los derivados de profármacos de los compuestos de la Fórmula (I) se preparan usando métodos conocidos por los expertos en el arte (por ejemplo, para más detalles, ver la referencia de Saulnier *et al.* (1994): *Bioorganic and Medicinal Chemistry Letters,* Vol. 4, p. 1985). Por ejemplo, los profármacos apropiados se preparan mediante la reacción de un compuesto no derivado de la Fórmula (I) con un agente de carbamilación adecuado (solo a modo de ejemplo, 1,1–aciloxialquilcarbanocloridato, para–nitrofenil carbonato, o similares).

En ciertas realizaciones, los compuestos de la Fórmula (I) se preparan como derivados protegidos usando métodos conocidos por los expertos en la materia. Una descripción detallada de las técnicas aplicables a la creación de

grupos protectores y su remoción puede hallarse en la referencia de T. W. Greene: *Protecting Groups in Organic Chemistry,*" 3ra. edición, John Wiley and Sons, Inc., 1999.

En ciertas realizaciones, los compuestos de la Fórmula (I) se preparan o se forman como solvatos (por ejemplo, hidratos). En ciertas realizaciones, los hidratos de compuestos de la Fórmula (I) se preparan mediante la recristalización a partir de una mezcla de solventes acuosa/orgánica, usando solventes orgánicos tales como dioxina, tetrahidrofurano o metanol.

En ciertas realizaciones, los compuestos de la Fórmula (I) se preparan como sus estereoisómeros individuales. En otras realizaciones, los compuestos de la Fórmula (I) que se describen en la presente solicitud se preparan como sus estereoisómeros individuales mediante la reacción de una mezcla racémica del compuesto con un agente de resolución ópticamente activo, a fin de formar un par de compuestos diastereoisómeros, la separación de los diastereómeros y la recuperación de los enantiómeros ópticamente puros. En ciertas realizaciones, la resolución de los enantiómeros se realiza usando derivados diastereómeros covalentes de los compuestos de la Fórmula (I), o mediante el uso de complejos disociables (por ejemplo, sales diastereómeras cristalinas). Los diastereómeros tienen propiedades físicas distintivas (por ejemplo, puntos de fusión, puntos de ebullición, solubilidad, reactividad, etc.), y se separan con facilidad sacando ventaja de estas diferencias. En ciertas realizaciones, los diastereómeros se separan mediante la cromatografía, o mediante técnicas de separación y resolución sobre la base de las diferencias en la solubilidad. El enantiómero ópticamente puro luego es recuperado, junto con el agente de resolución, por cualquier medio práctico que no logre la racemización. Una descripción más detallada de las técnicas aplicables a la resolución de estereoisómeros de compuestos a partir de su mezcla racémica puede hallarse en la referencia de

Jean Jacques, Andre Collet, Samuel H. Wilen: *Enantiomers, Racemates and Resolutions"* John Wiley and Sons, Inc., 1981.

Los compuestos de la Fórmula (I) se preparan mediante procesos descriptos en la presente solicitud e ilustrados en los Ejemplos. En ciertas realizaciones, los compuestos de la Fórmula (I) se preparan por medio de:

(a) la conversión opcional de un compuesto de la Fórmula (I) en una sal aceptable para uso farmacéutico;

(c) la conversión opcional de una forma de sal de un compuesto de la Fórmula (I) en una forma no salina;

(d) la conversión opcional de una forma no oxidada de un compuesto de la Fórmula (I) en un N–óxido farmacéuticamente aceptable;

(e) la conversión opcional de una forma de N–óxido de un compuesto de la Fórmula (I) en su forma no oxidada;

(f) la resolución opcional de un isómero individual de un compuesto de la Fórmula (I) a partir de una mezcla de isómeros;

(g) la conversión opcional de un compuesto no derivado de la Fórmula (I) en un derivado de profármaco aceptable para uso farmacéutico; y

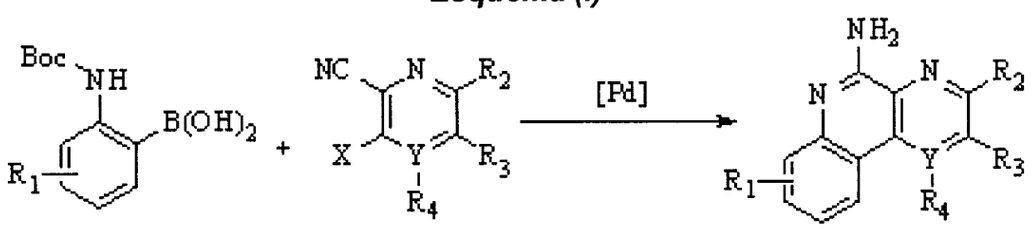
(h) la conversión opcional de un derivado de profármaco de un compuesto de la Fórmula (I) en su forma no derivada.

Ejemplos no limitativos de esquemas de síntesis utilizados para la elaboración de compuestos de la Fórmula (I) descriptos en esta solicitud se ilustran en los esquemas de reacción (I)–(XI).

El esquema (I) ilustra la síntesis de benzonaftiridinas (**3**) por medio del acoplamiento de ácidos 2–(*ter*–butoxicarbonil–amino)fenilbóricos (**1**) sustituidos o no sustituidos, con derivados de 3–halopicolinonitrilo (**2**) sustituidos o no sustituidos, en presencia de un catalizador de paladio. Solo a modo de ejemplo, la porción halo de los derivados de 3–halopicolinonitrilo es bromo o cloro. Los

grupos funcionales (R_1, R_2, R_3, R_4) en benzonaftiridinas (**3**) se modifican adicionalmente de manera opcional, como se describe en la presente solicitud.

Esquema (I)

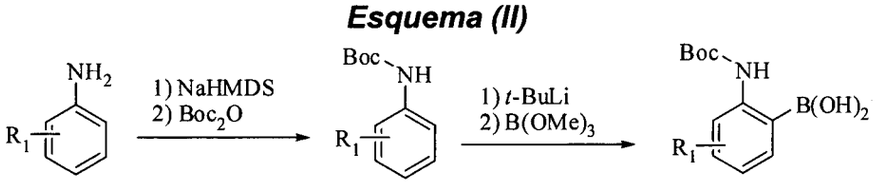


1 **2** **3**

X = Br o Cl
Y = C o N

En ciertas realizaciones, los ácidos fenilbóricos utilizados en la síntesis de compuestos de la Fórmula (I) se sintetizaron de acuerdo con el Esquema (II). En el Esquema (II), las anilinas sustituidas o no sustituidas (**4**) son Boc–protegidas en condiciones alcalinas, para obtener (**5**), y luego se convierten en los ácidos bóricos (**1**) a través de la orto–litiación y la reacción con trimetilborato, seguida del trabajo acuoso.

Esquema (II)



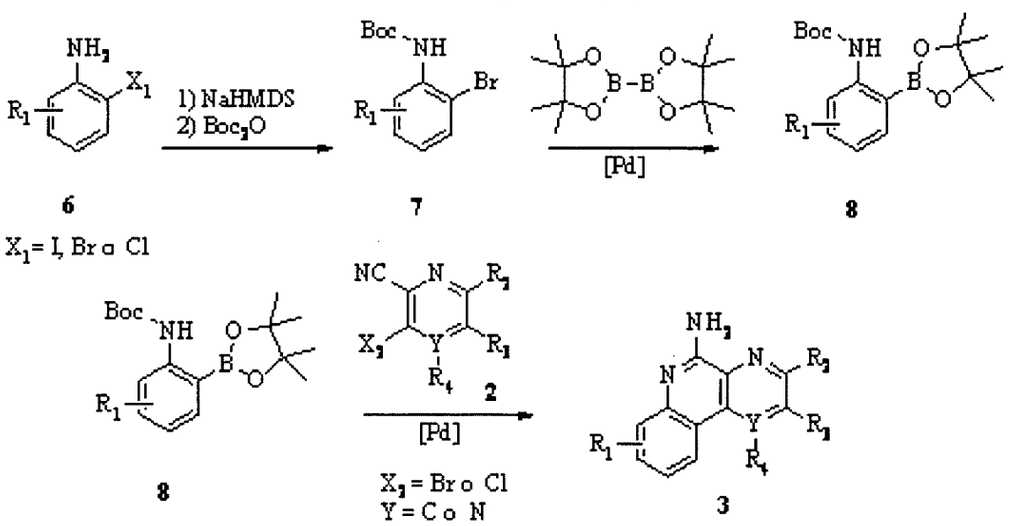
4 **5** **1**

Los ácidos bóricos (**1**) se usan como en el Esquema (I) y se hacen reaccionar con cianopiridinas (**2**) sustituidas o no sustituidas, a fin de lograr benzonaftiridinas (**3**) sustituidas o no sustituidas.

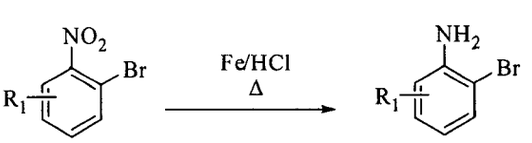
En ciertas realizaciones, se usaron equivalentes de ácido bórico, que incluyen, sin limitación, ésteres de boronato sustituidos o no sustituidos, en la síntesis de compuestos de la Fórmula (I). El Esquema (III) ilustra la síntesis de dichos ésteres de boronato sustituidos o no sustituidos (**8**), que se usan como

equivalentes de ácido bórico en la síntesis de benzonaftiridinas (**3**) sustituidas o no sustituidas. En el Esquema (III), las 2–haloanilinas (**6**) sustituidas o no sustituidas son Boc–protegidas en condiciones alcalinas, a fin de obtener (**7**), que luego se convierten en los ésteres de boronato sustituidos o no sustituidos (**8**) usando catálisis mediada con paladio. Estos ésteres de boronato (**8**) se usan como en el Esquema (I) y se hacen reaccionar con cianopiridinas sustituidas o no sustituidas (**2**) para lograr las benzonaftiridinas (**3**) sustituidas o no sustituidas.

Esquema (III)

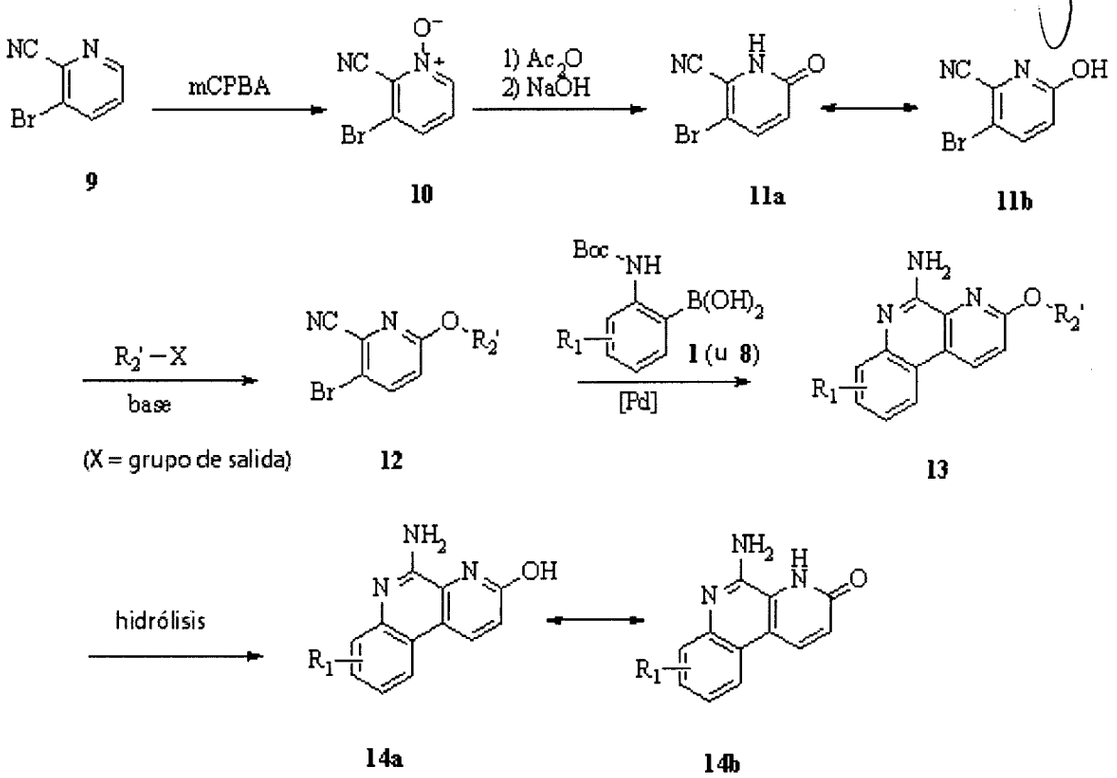


En ciertas realizaciones, se sintetizaron 2–bromoanilinas sustituidas o no sustituidas utilizadas en el Esquema (III), a partir de sus correspondientes compuestos de nitrobenceno sustituidos o no sustituidos como se ilustra a continuación.



En ciertas realizaciones, los compuestos de la Fórmula (I) que tienen sustituyentes ligados a oxígeno se sintetizaron usando las metodologías que se describen en el Esquema (IV).

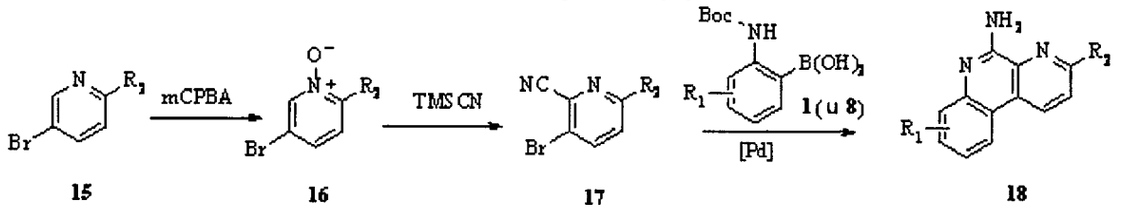
Esquema (IV)



En el Esquema (IV), en primer lugar, se oxida benzonitrilo (**9**) hasta el N–óxido (**10**) ácido meta–cloroperbenzoico (mCPBA), y luego se convierte en piridona (**11**). En condiciones alcalinas específicas, la piridona (**11**) se selectivamente alquilada en el oxígeno, a fin de obtener el alcoxipicolinonitrilo (**12**). Usando condiciones mediadas con paladio, como en el Esquema (I), los derivados de alcoxipicolinonitrilo (**12**) son acoplados con ácidos bóricos sustituidos o no sustituidos (**1**) (o ésteres de boronato sustituidos o no sustituidos (**8**)), a fin de obtener benzonaftiridina (**13**) sustituida o no sustituida con sustituyentes ligados a oxígeno. En ciertas realizaciones, la benzonaftiridina (**13**) con sustituyentes ligados a oxígeno se hidrolizó a fin de obtener la correspondiente benzonaftiridona (**14**).

En otras realizaciones, los compuestos de la Fórmula (I) que tienen diversos sustituyentes se sintetizaron usando la metodología descripta en el Esquema (V).

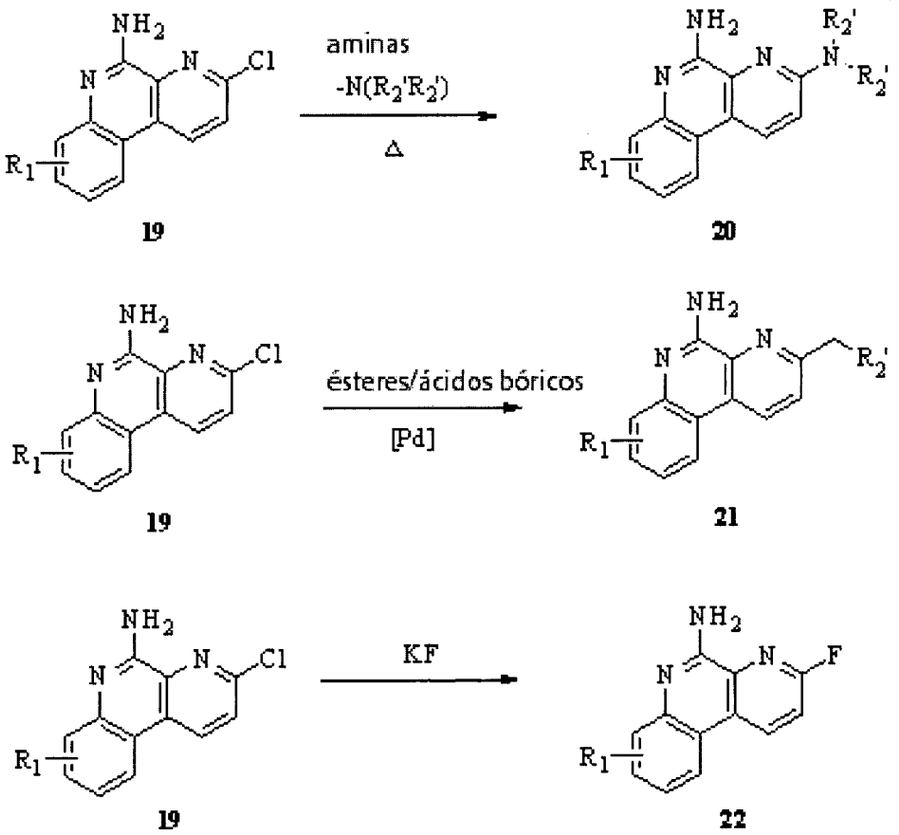
Esquema (V)



En el Esquema (V), en primer lugar, se oxidan 5–bromopiridinas (**15**) sustituidas en la posición 2 (expuesto como R_2 en el Esquema (V)) por ácido meta–cloroperbenzoico (mCPBA), a fin de obtener el N–óxido **16**, que luego se convierte en el benzonitrilo (**17**). Usando condiciones mediadas con paladio, como en el Esquema (I), los derivados de benzonitrilo (**17**) son acoplados con ácidos bóricos sustituidos o no sustituidos (**1**) (o ésteres de boronato sustituidos o no sustituidos (**8**)) a fin de obtener benzonaftiridina (**18**) no sustituida o sustituida con diversos sustituyentes en la posición 3. En otras realizaciones, la benzonaftiridina que tiene diversos sustituyentes en la posición 2 se obtiene iniciando con 5–bromopiridinas sustituidas en la posición 3.

En ciertas realizaciones, el sustituyente en la posición 3 de la benzonaftiridina (**18**) es un átomo de cloro, y esta 3–cloro–benzonaftiridina (**19**) es adicionalmente modificada de manera de obtener otros sustituyentes en la posición 3 de las benzonaftiridinas. Ejemplos no limitativos de dichas modificaciones se ilustran en el Esquema (VI).

Esquema (VI)

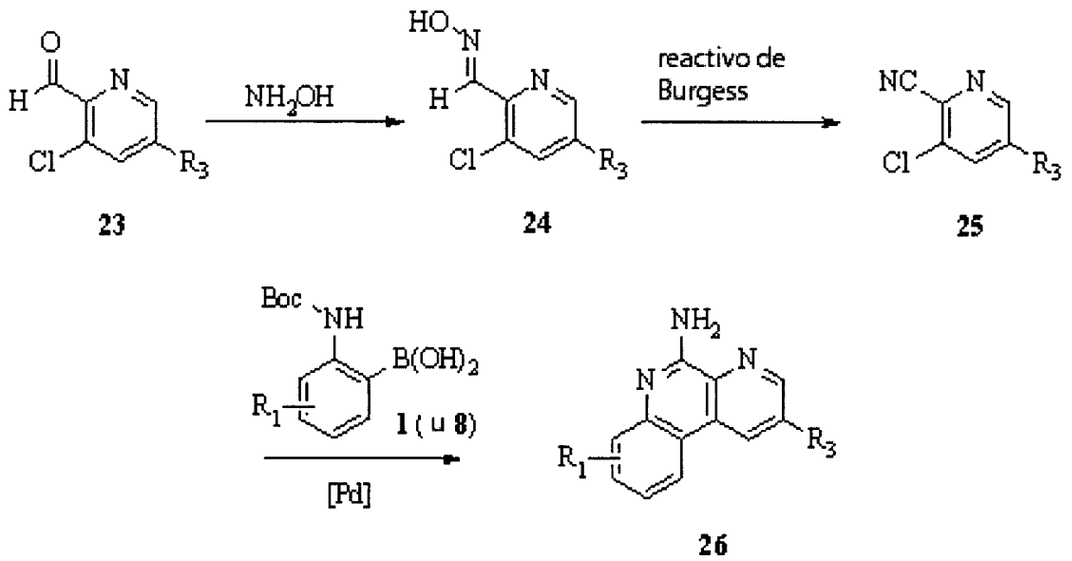


En ciertas realizaciones, como se ilustra en el Esquema (VI), los compuestos de la Fórmula (I) que tienen sustituyentes N–ligados (derivados de (**20**)) se obtuvieron por medio de reacciones S_NAr, mediante el calentamiento de dichos cloro–derivados (**19**) con diversas aminas. En ciertas realizaciones, como se ilustra en el Esquema (VI), los compuestos de la Fórmula (I) que tienen sustituyentes carbono–ligados (derivados de (**21**)) se obtuvieron por medio de acoplamientos de Suzuki, usando condiciones mediadas con paladio con diversos ácidos bóricos o ésteres de boronato. En ciertas realizaciones, como se ilustra en el Esquema (VI), los compuestos de la Fórmula (I) se fluoraron mediante el tratamiento de dichos cloro–derivados (**19**) con fluoruro de potasio, de manera de obtener (3–fluorbenzo[f][1,7]–naftiridin–5–amina (**22**)).

En otras realizaciones, los compuestos de la Fórmula (I) que tienen diversos sustituyentes se sintetizaron usando la metodología descripta en el

Esquema (VII).

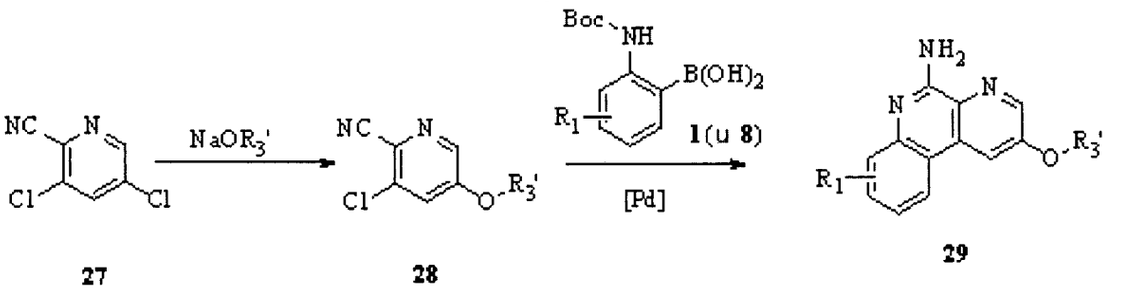
Esquema (VII)



En el Esquema (VII), 3–clorobenzaldehído (**23**) (con un sustituyente R_3 en la posición 5) se convierte primero en la correspondiente hidroxilamina (**24**), que luego se usa para la elaboración del correspondiente nitrilo (**25**). Usando condiciones mediadas con paladio, como en el Esquema (I), los derivados de nitrilo (**25**) se acoplan con ácidos bóricos sustituidos o no sustituidos (**1**) (o ésteres de boronato sustituidos o no sustituidos (**8**)), a fin de obtener la benzonaftiridina (**26**) con diversos sustituyentes en la posición 2.

En otras realizaciones, ciertos compuestos de la Fórmula (I) que tienen sustituyentes ligados a oxígeno se sintetizaron usando la metodología que se describe en el Esquema (VIII).

Esquema (VIII)

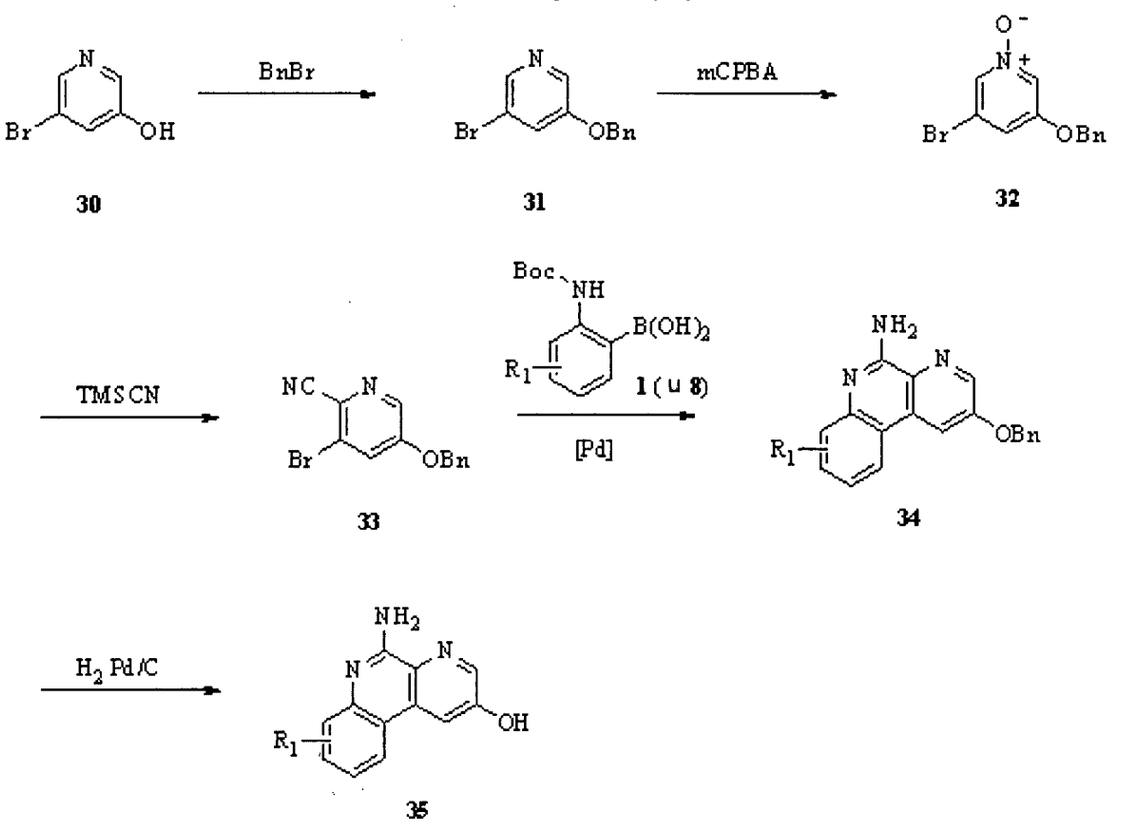


27 **28** **29**

En el Esquema (VIII), las benzonaftiridinas con diversos sustituyentes R_3 ligados a oxígeno en la posición 2 se preparan usando un 3,5–dihalopicolinonitrilo, tal como, solo a modo de ejemplo, 3,5–dicloropicolinonitrilo (**27**), que primero es monosustituido con un apéndice de alcoxi a fin de obtener el correspondiente picolinonitrilo (**28**). A continuación, usando condiciones mediadas con paladio como en el Esquema (I), los derivados de nitrilo (**27**) son acoplados con ácidos bóricos sustituidos o no sustituidos (**1**) (o ésteres de boronato sustituidos o no sustituidos (**8**)) a fin de obtener la benzonaftiridina (**29**) con diversos sustituyentes ligados a oxígeno en la posición 2.

En ciertas realizaciones, los compuestos de la Fórmula (I) que tienen sustituyentes hidroxi, que incluyen sustituyentes benzonaftiridinas hidroxi en la posición 2, se prepararon usando la vía de síntesis que se muestra en el Esquema (IX).

Esquema (IX)

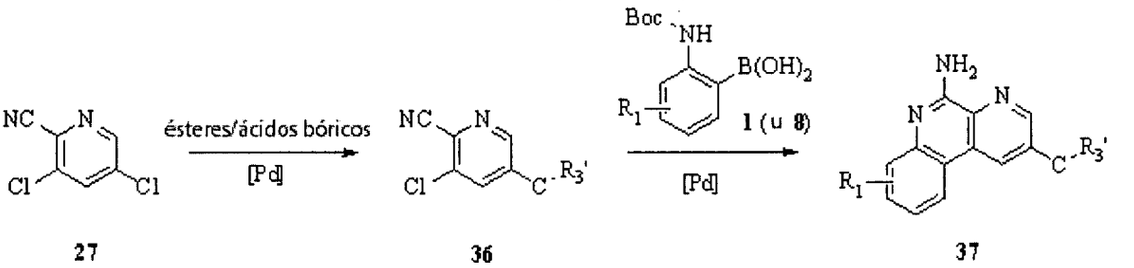


En el Esquema (IX), un 5–halopiridin–3–ol, tal como, solo a modo de ejemplo, 3,5–bromopiridin–3–ol (**30**), es bencil–protegido en el grupo hidroxilo, a fin de obtener (**31**), que luego es convertido en el correspondiente N–óxido (**32**). El N–óxido (**32**) es adicionalmente convertido en el nitrilo (**33**). A continuación, usando condiciones mediadas con paladio como en el Esquema (I), los derivados de nitrilo (**33**) son acoplados con ácidos bóricos sustituidos o no sustituidos (**1**) (o ésteres de boronato sustituidos o no sustituidos (**8**)), a fin de obtener la benzonaftiridina (**34**), que con la hidrogenación, proporciona la benzonaftiridina (**35**) con un sustituyente hidroxilo en la posición 2.

En otras realizaciones, ciertos compuestos de la Fórmula (I) que tienen sustituyentes ligados a carbono, que incluyen benzonaftiridinas con diversos sustituyentes ligados a carbono en la posición 2, se prepararon usando la vía de

síntesis que se muestra en el Esquema (X).

Esquema (X)

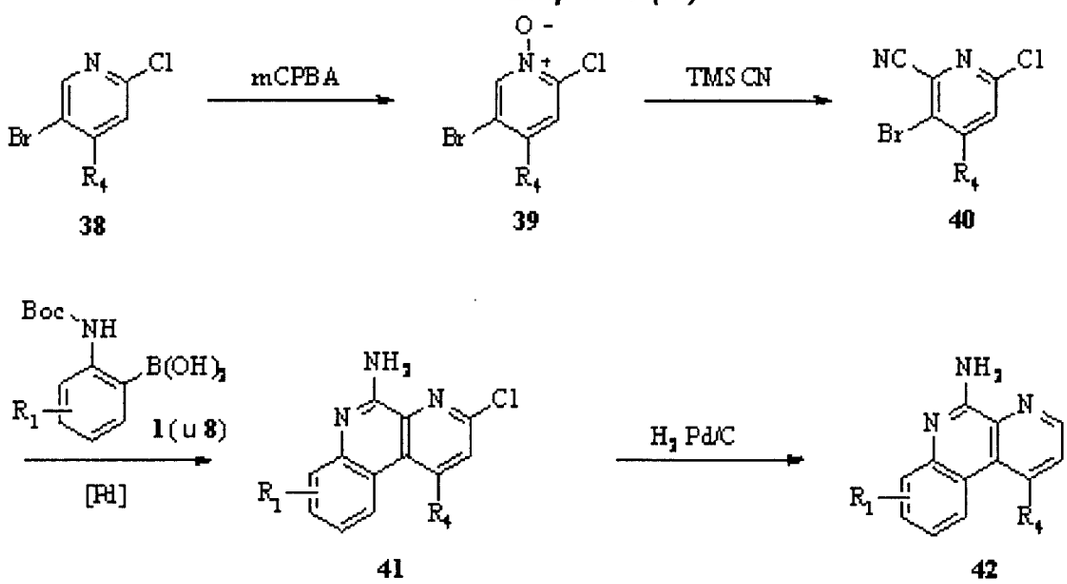


27 36 37

En el Esquema (X), un 3,5–dihalopicolinonitrilo, tal como, a modo de ejemplo solamente, 3,5–dicloropicolinonitrilo (**27**), es primero monosustituido usando un equivalente de éster/ácido bórico, a fin de obtener el correspondiente picolinonitrilo (**36**). Usando condiciones mediadas con paladio más vigorosas como en el Esquema (I), los derivados de nitrilo (**36**) son acoplados con ácidos bóricos sustituidos o no sustituidos (**1**) (o ésteres de boronato sustituidos o no sustituidos (**8**), a fin de obtener la benzonaftiridina (**37**) que tiene sustituyentes ligados a carbono en la posición 2. En ciertas realizaciones, el sustituyente ligado a carbono es un alqueno, mientras que en otras realizaciones, dichos alquenos son adicionalmente modificados mediante la hidrogenación, a fin de obtener benzonaftiridinas con grupos alquilo en la posición 2.

En otras realizaciones, ciertos compuestos de la Fórmula (I) que tienen diversos sustituyentes, que incluyen benzonaftiridinas con diversos sustituyentes en la posición 1, se sintetizaron usando la metodología que se describe en el Esquema (XI).

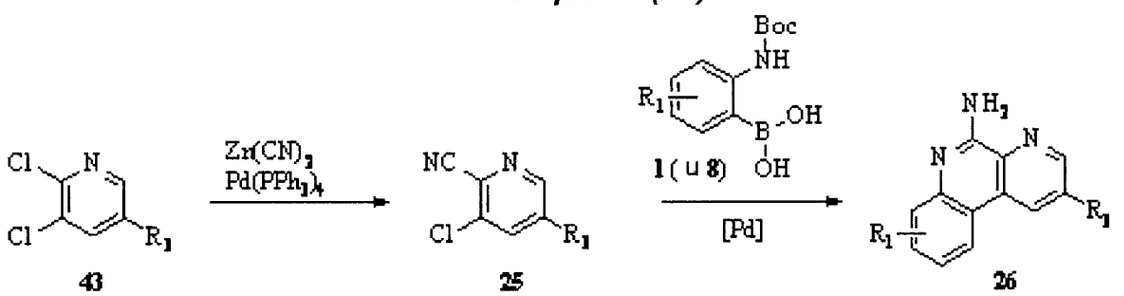
Esquema (XI)



En el Esquema (XI), una 2,5–dihalopiridina sustituida en la posición 4, tal como, solo a modo de ejemplo, 5–bromo–2–cloropiridina (**38**), primero se convierte en el correspondiente N–óxido (**39**), que luego se convierte en el correspondiente nitrilo (**40**). Usando condiciones mediadas con paladio, como en el Esquema (I), los derivados de nitrilo (**40**) son acoplados con ácidos bóricos sustituidos o no sustituidos (**1**) (o ésteres de boronato sustituidos o no sustituidos (**8**)), de manera de obtener la benzonaftiridina (**41**) que tiene sustituyentes en la posición 1. En ciertas realizaciones, la benzonaftiridina (**41**) es adicionalmente desclorada a fin de obtener benzonaftiridina (**42**).

En otras realizaciones, ciertos compuestos de la Fórmula (I) que tienen diversos sustituyentes, que incluyen benzonaftiridinas con diversos sustituyentes en la posición 2, se sintetizaron usando la metodología descripta en el Esquema (XII).

Esquema (XII)

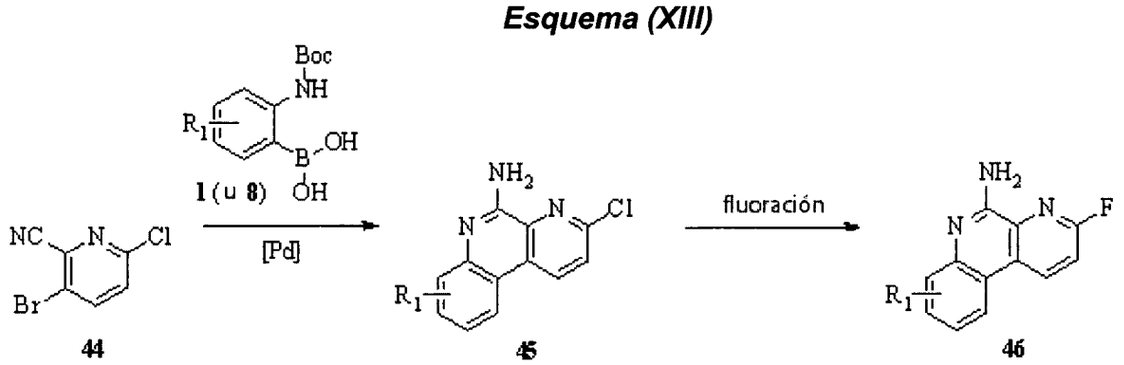


43 **25** **26**

En el Esquema (XII), una 2,3–dihalopiridina sustituida en la posición 5 (**43**), tal como, solo a modo de ejemplo, (5,6–dicloropiridin–3–il)metanol, es primero convertida en el correspondiente nitrilo (**25**). Usando condiciones mediadas con paladio como en el Esquema (I), los derivados de nitrilo (**25**) son acoplados con ácidos bóricos sustituidos o no sustituidos (**1**) (o ésteres de boronato sustituidos o no sustituidos (**8**)), a fin de obtener la benzonaftiridina (**26**) que tiene sustituyentes en la posición 2.

Se prepararon diversas 3–halo naftiridinas de acuerdo con los métodos generales ejemplificados en el Esquema XIII.

Esquema (XIII)



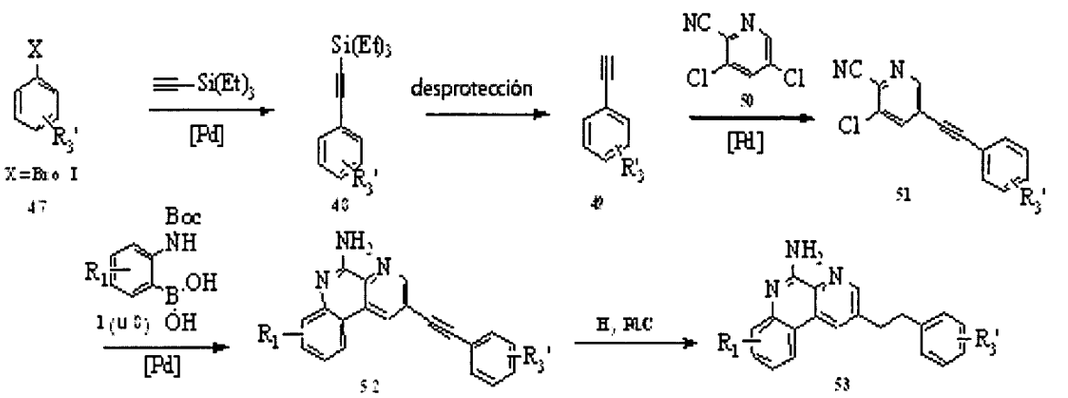
44 **45** **46**

En el Esquema (XIII), usando condiciones mediadas con paladio como en el Esquema (I), una 3,6–dihalo–2–cianopiridina, tal como, solo a modo de ejemplo, 3–bromo–6–cloropicolinonitrilo, se acopla con ácidos bóricos sustituidos o no sustituidos (**1**) (o ésteres de boronato sustituidos o no sustituidos (**8**)), a fin de obtener la benzonaftiridina (**45**) que tiene sustituciones de halógeno en la posición 3. El intercambio de halógeno adicional de benzonaftiridina (**45**)

proporcionó benzonaftiridina (**46**) con diferentes sustituyentes de halógeno en la posición 3.

En otras realizaciones, ciertos compuestos de la fórmula (I) se sintetizaron usando la metodología que se describe en el Esquema (XIV).

Esquema (XIV)

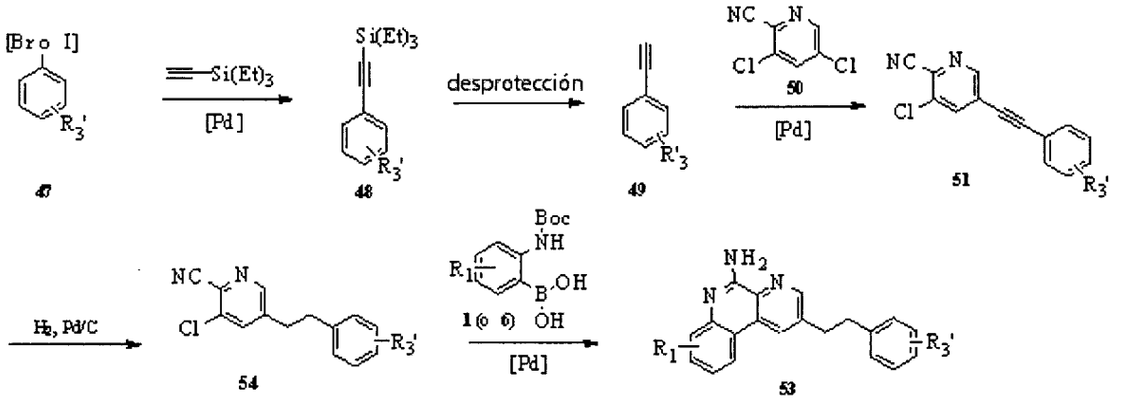


En el Esquema (XIV), se acoplan bromuros de arilo o yoduros de arilo (**47**) sustituidos con diversos grupos R_3' con trietil(etinil)silano (o sus equivalentes), usando condiciones mediadas con paladio, a fin de obtener **48**. Luego de la desprotección del grupo de protección de sililo, los derivados de acetileno (**49**) son acoplados con 3,5–dicloropicolinonitrilo (**50**) usando condiciones mediadas con paladio, a fin de lograr 3–cloro–2–cianopiridinas (**51**). Los derivados de **51**, tales como, solo a modo de ejemplo, 3–cloro–5–(feniletinil)picolinonitrilo, se acoplan con ácidos bóricos sustituidos o no sustituidos (**1**) (o ésteres de boronato sustituidos o no sustituidos (**8**)), a fin de obtener la benzonaftiridina (**52**). El compuesto **52** luego se somete a condiciones de hidrogenación, de manera de obtener benzonaftiridinas **53** con diferentes sustituyentes en la posición R_3'.

En otras realizaciones, ciertos compuestos de la Fórmula (I) se sintetizaron

usando la metodología que se describe en el Esquema (XV).

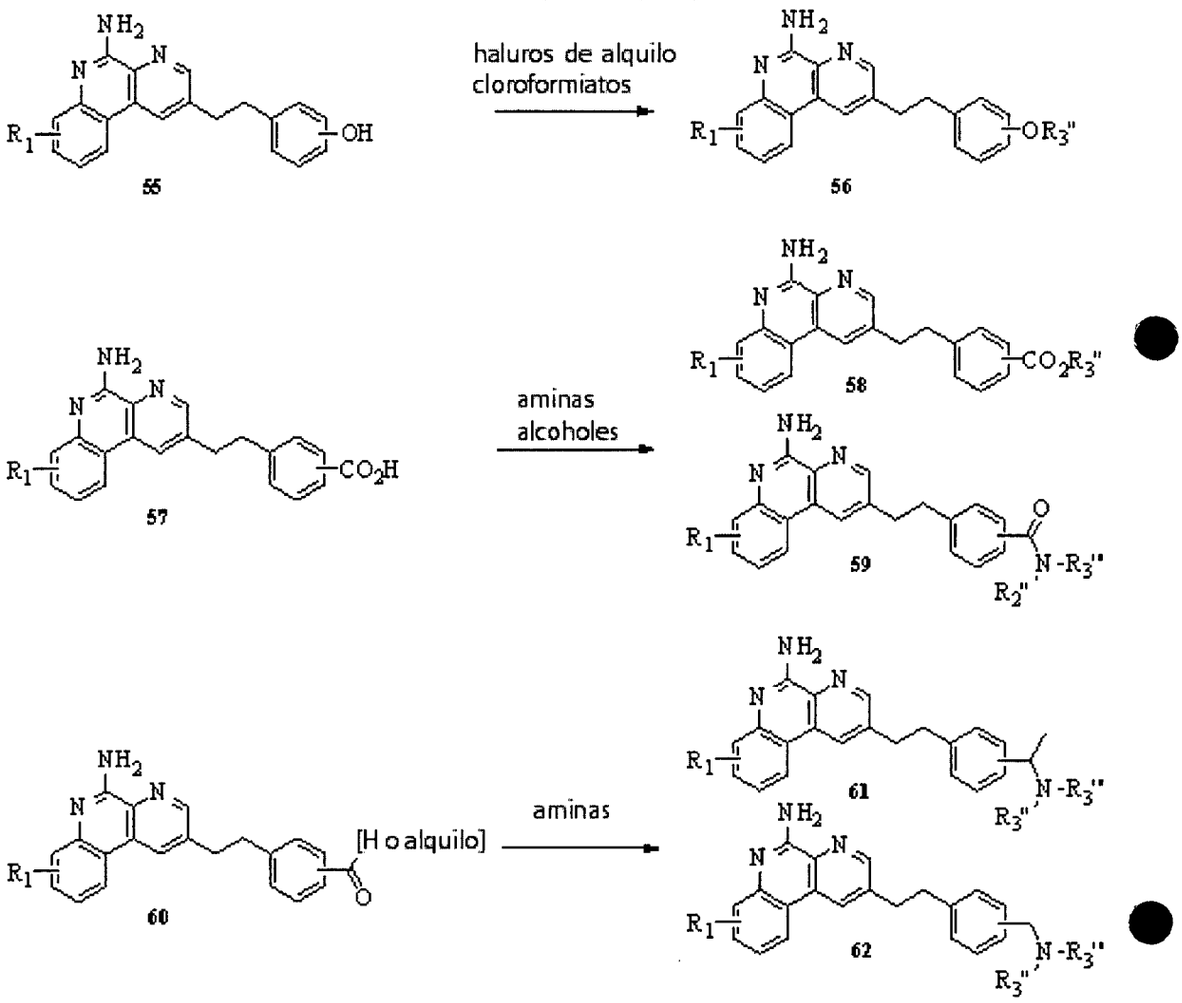
Esquema (XV)



En el Esquema (XV), se acoplan bromuros de arilo o yoduros de arilo (**47**) sustituidos con diversos grupos R_3', con trietil(etinil)silano (o sus equivalentes), usando condiciones mediadas con paladio para lograr **48**. Luego de la desprotección del grupo de protección de sililo, los derivados de acetileno (**49**) se acoplan con 3,5–dicloropicolinonitrilo (**50**) usando condiciones mediadas con paladio a fin de lograr 3–cloro–2–cianopiridinas (**51**). Los derivados de **51** tales como, solo a modo de ejemplo, 3–cloro–5–(feniletinil)picolinonitrilo, se reducen hasta el correspondiente 3–cloro–5–fenetilpicolinonitrilo (**54**) en condiciones de hidrogenación. El compuesto **54** se acopla con ácidos bóricos sustituidos o no sustituidos (**1**) (o ésteres de boronato sustituidos o no sustituidos (**8**)), a fin de obtener benzonaftiridinas **53** con diferentes sustituyentes en la posición R_3'.

Las benzonaftiridinas con diversas sustituciones pueden ser adicionalmente convertidas en otros grupos funcionales usando transformaciones orgánicas estándares. En ciertas realizaciones, ciertos compuestos de la Fórmula (I) se sintetizaron usando la metodología que se describe en el Esquema (XVI).

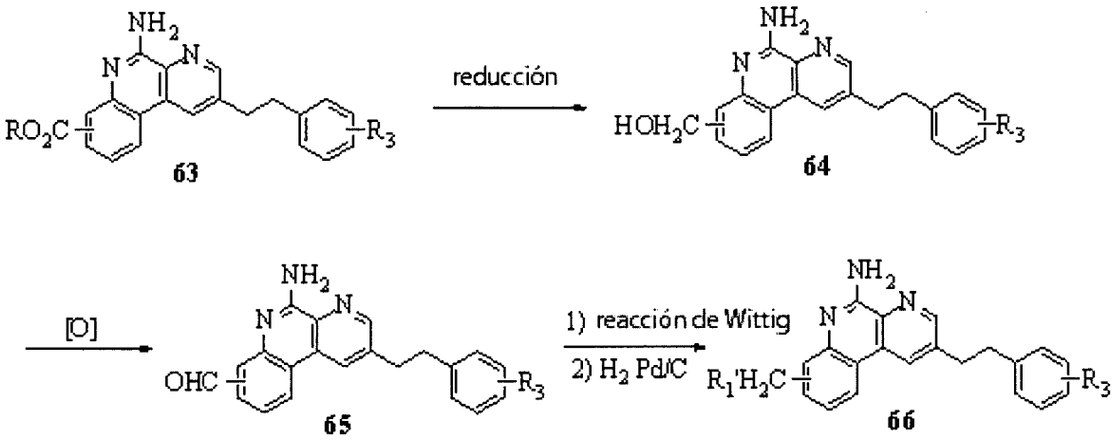
Esquema (XVI)



A modo de ejemplo, en el Esquema (XVI), las benzonaftiridinas que portan un grupo hidroxilo (**55**) son convertidas en los correspondientes éteres o carbonatos (**56**). Por ejemplo, las benzonaftiridinas que portan un grupo ácido carboxílico (**57**) son convertidas en los correspondientes ésteres (**58**) o las amidas (**59**). Por ejemplo, las benzonaftiridinas que portan un grupo aldehído o cetona (**60**) se convierten en las correspondientes aminas (**61** ó **62**). Estas benzonaftiridinas pueden ser adicionalmente modificadas usando las transformaciones orgánicas estándares.

En ciertas realizaciones, ciertos compuestos de la Fórmula (I) se sintetizaron usando la metodología que se describe en el Esquema (XVII).

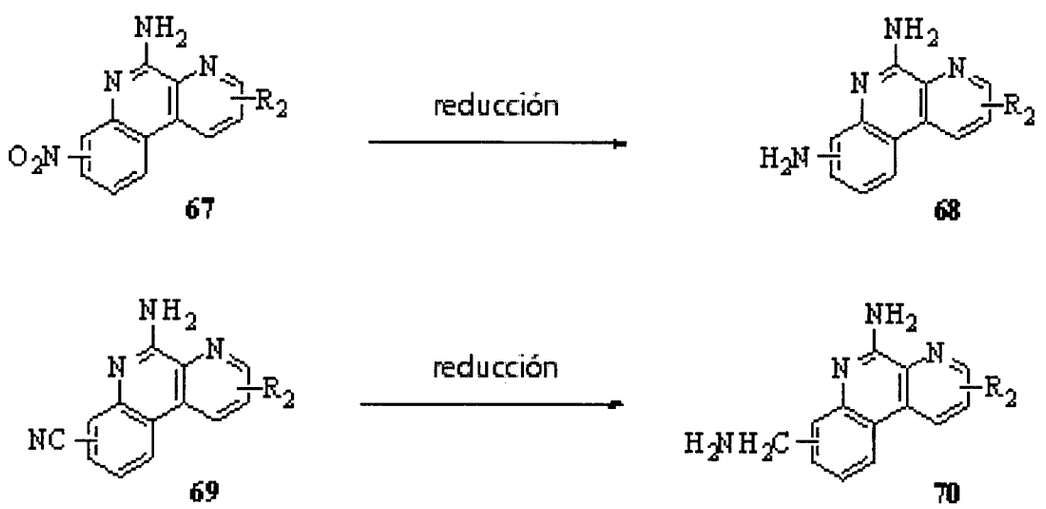
Esquema (XVII)



En el Esquema (XVII), las benzonaftiridinas con diversas sustituciones son adicionalmente convertidas en diferentes grupos funcionales a través de transformaciones orgánicas estándares. Por ejemplo, las benzonaftiridinas que portan un grupo éster (**63**) son convertidas en el correspondiente alcohol (**64**) mediante la reducción usando agentes de reducción estándares. El compuesto **64** es oxidado hasta el correspondiente aldehído (**65**), que es adicionalmente alquilado por medio de una reacción de Wittig seguida de la hidrogenación a fin de obtener los derivados **66**. Estas benzonaftiridinas pueden ser adicionalmente modificadas empleando transformaciones orgánicas estándares.

En ciertas realizaciones, ciertos compuestos de la Fórmula (I) se sintetizaron usando la metodología que se describe en el Esquema (XVIII).

Esquema (XVIII)

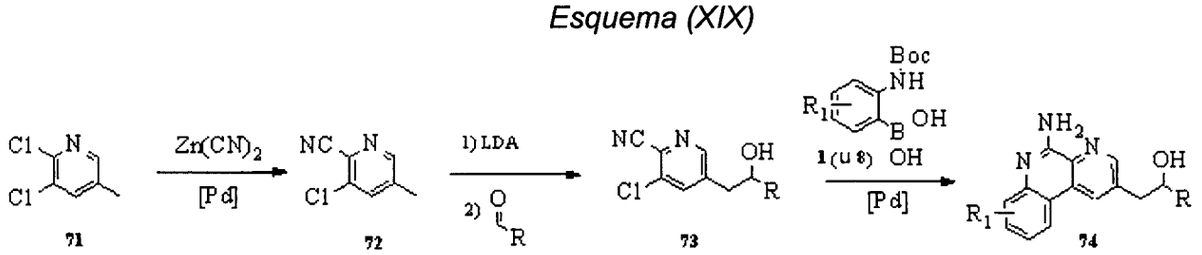


67 68 69 70

En el Esquema (XVIII), las benzonaftiridinas con diversas sustituciones se convierten adicionalmente en diferentes grupos funcionales a través de transformaciones orgánicas convencionales. Por ejemplo, las benzonaftiridinas que portan un grupo nitro (**67**) o un grupo ciano (**69**) son convertidas en la correspondiente amina (**68**) o metil amina (**70**) mediante la reducción usando agentes de reducción estándares. Estas benzonaftiridinas pueden modificarse adicionalmente usando las transformaciones orgánicas estándares.

En ciertas realizaciones, ciertos compuestos de la Fórmula (I) se sintetizaron usando la metodología que se describe en el Esquema (XIX).

Esquema (XIX)



71 72 73 74

En el Esquema (XIX), 2,3–dicloro–5–metilpiridina (**71**) se convierte en el correspondiente nitrilo (**72**). El alcohol **73** se forma en condiciones de condensación de Aldol, donde el compuesto **72** reacciona con un aldehído o una cetona. Los derivados de **73** son luego acoplados con ácidos bóricos (**1**) o ésteres

de boronato (**8**) a fin de obtener la benzonaftiridina (**74**).

Los siguientes ejemplos se ofrecen de manera de ilustrar, y no de limitar, los compuestos de la Fórmula (I) que aquí se proveen, y la preparación de dichos compuestos.

Farmacología y utilidad.

Cuando un antígeno extraño desafía el sistema inmunitario, este responde lanzando una respuesta protectora, que se caracteriza por la interacción coordinada tanto del sistema inmunitario innato como del adquirido. Estos dos sistemas interdependientes cumplen dos requisitos mutuamente exclusivos: velocidad (contribuida por el sistema innato) y especificidad (contribuida por el sistema de adaptación).

El sistema inmunitario innato sirve como la primera línea de defensa contra la invasión de patógenos, manteniendo al patógeno bajo control, mientras las respuestas de adaptación maduran. Se dispara dentro de los primeros minutos de infección de una manera independiente del antígeno, respondiendo a patrones ampliamente conservados en los patógenos (si bien no es no específico, y puede distinguir entre lo propio y los patógenos). De manera crucial, genera además el medio inflamatorio y coestimulante (a veces, denominado la señal de peligro) que potencia el sistema inmunitario de adaptación y lo conduce (o polariza) hacia las respuestas celulares o humorales más apropiadas para combatir el agente infeccioso. El desarrollo de moduladores de TLR para el direccionamiento terapéutico de la inmunidad innata ha sido reseñado (ver las referencias: *Nature Medicine*, 2007; 13; 552–559; *Drug Discovery Today: Therapeutic Strategies,* 2006, 3, 343–352; y *Journal of Immunology,* 2005; 174; 1259–1268).

La respuesta de adaptación se torna efectiva durante días o semanas, si bien, en última instancia, proporciona la especificidad antigénica refinada requerida para la eliminación completa del patógeno y la generación de memoria

inmunológica. Es mediada, principalmente, por células T y B que han pasado por la redisposición de genes de línea germinal y que se caracterizan por la especificidad y la memoria de largo plazo. Sin embargo, además involucra el reclutamiento de elementos del sistema inmunitario innato, que incluyen fagocitos profesionales (macrófagos, neutrófilos, etc.) y granulocitos (basófilos, eosinófilos, etc.) que rodean bacterias y aun parásitos protozoos relativamente grandes. Una vez que la respuesta del sistema inmunitario de adaptación ha madurado, la posterior exposición al patógeno logra su rápida eliminación, debido a las células de memoria altamente específica que han sido generadas y que son rápidamente activadas con la posterior exposición a su antígeno cognado.

Las enfermedades autoinmunitarias se definen por: (i) la respuesta humoral o de autoanticuerpo a un antígeno propio (solo a modo de ejemplo, el hipertiroidismo primario de Grave con anticuerpos para el receptor de TSH); o (ii) la respuesta celular donde las células inmunitarias destruyen células no inmunitarias de las cuales deriva el antígeno propio (solo a modo de ejemplo, el tirocito (tiroiditis de Hashimoto) o la célula pancreática de islote β (diabetes tipo 1)). Muchas enfermedades autoinmunitarias son una combinación de ambos fenómenos, por ejemplo, la enfermedad de Hashimoto y la diabetes tipo 1 también tienen autoanticuerpos, peroxidasa antitiroidea (TPO, por sus siglas en inglés) o ácido antiglutámico decarboxilasa (GAD)/islote. Las enfermedades autoinmunitarias a menudo tienen un componente inflamatorio, que incluye, sin limitación, incrementos en las moléculas de adhesión (solo a modo de ejemplo, la molécula 1 de adhesión celular vascular (VACM–1) y la alterada adhesión de leucocitos a la vasculatura, tal como, solo a modo de ejemplo, colitis, lupus sistémico, esclerosis sistémica y las complicaciones vasculares de la diabetes.

Los receptores de tipo toll (TLR) son proteínas de transmembrana tipo I caracterizadas por un dominio de repetición rica en leucina N–terminal

extracelular (LRR, por sus siglas en inglés), seguido de una región rica en cisteína, un dominio TM y una cola intracelular (citoplásmica) que contiene una región conservada denominada el dominio Toll/IL–1 (TIR, por sus siglas en inglés). Los TLR son receptores de reconocimiento de patrones (PRR, por sus siglas en inglés) expresados principalmente en células inmunitarias, que incluyen, sin limitación, células dendríticas, linfocitos T, macrófagos, monocitos y linfocitos citolíticos naturales. El dominio LLR es importante para la unión de ligando y la señalización asociada, y es un rasgo común de los PRR. El dominio TIR es importante en las interacciones de proteína–proteína, y se asocia con la inmunidad innata. El dominio TIR además une una superfamilia mayor de IL–1 R/TLR que se compone de tres subgrupos. Los miembros del primer grupo poseen dominios de inmunoglobulina en sus regiones extracelulares, e incluyen receptores IL–1 e IL–18 y proteínas accesorias, al igual que ST2. El segundo grupo abarca los TLR. El tercer grupo incluye proteínas de adaptación intracelulares importantes para la señalización.

Los TLR son un grupo de receptores de reconocimiento de patrones que se unen a patrones moleculares asociados a patógenos (PAMPS, por sus siglas en inglés) de bacterias, hongos, protozoos y virus, y actúan como una primera línea de defensa contra patógenos invasores. Los TLR son esenciales para la inducción de la expresión de genes involucrados en respuestas inflamatorias, y los TLR y el sistema inmunitario innato son una etapa decisiva en el desarrollo de la inmunidad adquirida específica de antígeno.

La inmunidad de adaptación (humoral o mediada por células) se asocia con el mecanismo de señal de TLR de la inmunidad innata. La inmunidad innata es una respuesta celular inmunitaria protectora que funciona rápidamente para luchar contra ataques ambientales que incluyen, sin limitación, agentes bacterianos o virales. La inmunidad de adaptación es una respuesta más lenta,

que involucra la diferenciación y activación de linfocitos T naturales en tipos celulares cooperadores T 1 (Th1) o cooperadores T 2 (Th2). Las células Th1 promueven principalmente la inmunidad celular, mientras que las células Th2 promueven la inmunidad humoral. Sin embargo, principalmente, en un sistema protector del huésped, la expresión patológica de las señales de inmunidad innata que emanan de la vía TLR están implicadas en el inicio de las enfermedades inflamatorias autoinmunitarias.

Todos los TLR parecen funcionar ya sea como un homodímero, ya sea como un heterodímero en el reconocimiento de un determinante específico, o un grupo de determinantes específicos moleculares presentes en organismos patógenos que incluyen lipopolisacáridos de superficie celular bacteriana, lipoproteínas, flagelina bacteriana, ADN tanto de bacterias como de virus y ARN viral. La respuesta celular a la activación de TLR involucra la activación de uno o más factores de transcripción, que conducen a la producción y secreción de citoquinas y moléculas coestimulantes tales como interferones, TNF–, interleuquinas, MIP–1 y MCP–1, que contribuyen a la muerte y el aclaramiento de la invasión patógena.

La expresión espacial de TLR es coincidente con la interfaz ambiental del huésped. Si bien solo pocas otras proteínas de tipo Toll han sido clonadas en *Drosophila*, la familia de TLR humanos está compuesta por al menos 11 miembros, TLR1 a TLR11, que producen respuestas biológicas de superposición, aunque distintas, debido a las diferencias en la expresión celular y las vías de señalización que inician. Cada uno de los TLR es expresado en un subgrupo diferente de leucocitos, y cada uno de los TLR es específico en sus patrones de expresión y sensibilidades de PAMP, y detecta subgrupos diferentes de patógenos que permiten la atenta vigilancia por el sistema inmunitario.

Receptor de tipo Toll 1 (TLR1).

TLR1 es cartografiado en el cromosoma 4p14, y su secuencia codifica una proteína putativa de 786 aminoácidos (aa) con 18 LRR N–terminales y un peso molecular calculado de 84 kDa. TLR1 se relaciona más estrechamente con TLR6 y TLR10, con 68% y 48% en total de identidad de secuencia (aa), respectivamente.

El ARNm de TLR1 es expresado en forma ubicua y es hallado en mayores niveles que los otros TLR. De las principales poblaciones de leucocitos, TLR1 es expresado en mayor cantidad por monocitos, aunque también es expresado por macrófagos, células dendríticas, leucocitos polimorfonucleares, células B, T y NK. *In vivo*, se observan dos transcripciones de tamaño diferente para TLR1, lo que sugiere que el ARNm es alternativamente empalmado para generar dos formas diferentes de la proteína. *In vitro,* el ARNm de TLR1 y la expresión de proteína son reguladas en forma ascendente en células leucémicas monocíticas (THP–1, por sus siglas en inglés), con la diferenciación inducida por PMA. La expresión de TLR1 es regulada en forma ascendente por IL–6 autocrino, y además, es elevada por IFN–γβ, IL–10 y TNF–α. Sin embargo, el nivel de TLR1 no es afectado por la exposición tanto a bacterias Gram positivas como Gram negativas. *Ex vivo*, la expresión de TLR1 tanto de monocitos como de granulocitos es regulada en forma descendente luego de la exposición a bacterias Gram–negativas. TLR1 forma un heterodímero con TLR2. TLR1 además heterodimeriza con TLR4, que inhibe la actividad de TLR4.

Receptor de tipo Toll 2 (TLR2)

TLR2 es cartografiado en el cromosoma 4q31–32, y codifica una proteína putativa de 784 aminoácidos (aa) con 19 LLR N–terminales y un peso molecular calculado de 84 kDa. TLR2 se relaciona más estrechamente con TLR6, con 31% en total de identidad de secuencia (aa).

La expresión de ARNm de TLR2 se observa en los tejidos del cerebro, el corazón, pulmón y el bazo, y es más alta en PBL, específicamente, aquellos de origen melanocítico. *In vivo*, se observan dos transcripciones de tamaño diferente para TLR2, lo que sugiere que el ARNm es alternativamente empalmado. *In vitro*, el ARNm de TLR2 y la expresión de proteína son regulados en forma ascendente en células leucémicas monocíticas (THP–1), con la diferenciación inducida por PMA. TLR2 es regulado en forma ascendente por IL–6 autocrino, TNF–α, IL–1β e IL–10. La expresión de ARNm de TLR2 es elevada luego de la exposición tanto a bacterias Gram positivas como Gram negativas. TLR2 forma heterodímeros con TLR1, TLR6 y, posiblemente, TLR10, donde cada complejo es particularmente sensible a los subgrupos de PAMP asociados con TLR2. Los complejos de TLR2 reconocen un amplio rango de PAMP, en su mayoría, de bacterias. Estos incluyen, sin limitación, lipoarabinomanano (LAM, por sus siglas en inglés), lipopolisacárido (LPS), ácido lipoteicoico (LTA, por sus siglas en inglés), peptidoglicano (PGN), y otros glicolípidos, glicoproteínas y lipoproteínas. Los complejos de TLR2 además pueden detectar virus, que incluyen, sin limitación, virus del sarampión (MV), citomegalovirus humano (HCMV) y virus de la hepatitis C (HCV) y PAMP fúngicos, que incluyen, sin limitación, zimosano. TLR2 reconoce una variedad de lipoproteínas/lipopétidos de diversos patógenos, tales como, a modo de ejemplo solamente, bacterias Gram positivas, micobacterias, *Tripanosoma cruzi,* hongos y *Treponema.* Además, TLR2 reconoce preparaciones de LPS de organismos no enterobacterianos, tales como, solo a modo de ejemplo, *Leptospira interrogans, Porphyromonas gingivalis* y *Helicobacter pylori.* Los complejos de TLR2 son capaces tanto de la detección de patrones no propios, como de la detección de patrones propios alterados, tales como aquellos exhibidos por células necróticas. TLR2 es reclutado para fagosomas, y se involucra en la internalización de productos microbianos por células.

Receptor de tipo Toll 3 (TLR3).

TLR3 es cartografiado en el cromosoma 4q35, y su secuencia codifica una proteína putativa de 904 (aa) con 24 LRR N–terminales y un peso molecular calculado de 97 kDa. TLR3 se relaciona más estrechamente con TLR5, TLR7 y TLR8, cada uno, con 26% en total de identidad de secuencia (aa).

El ARNm de TLR3 se expresa en mayores niveles en la placenta y el páncreas. TLR3 es expresado por células dendríticas, células T y NK. *In vivo*, se observan dos transcripciones de tamaño diferente para TLR3, lo que sugiere que el ARNm es alternativamente empalmado para generar dos formas diferentes de la proteína. *In vitro*, THP–1 TLR3 diferenciado por PMA es moderadamente regulado en forma ascendente por IFN–γ autocrino, IL–1β, IL–6, IL–10 y TNF–α. EL ARNm de TLR3 es elevado luego de la exposición a bacterias Gram negativas, y aun hasta un grado mayor, en respuesta a bacterias Gram positivas. *Ex vivo*, la expresión de TLR3 es elevada tanto en monocitos como en granulocitos con la exposición a bacterias Gram negativas. TLR3 forma un homodímero y reconoce ARN de doble hebra viral (ARNds). Si bien se da generalmente por sentado que los TLR se expresan sobre la superficie celular, aquellos TLR sensibles a los PAMP internos, tales como ARNds en el caso de TLR3, se ubican intracelularmente en el compartimiento liosómico.

Receptor de tipo Toll 4 (TLR4).

TLR4 es cartografiado en el cromosoma 9q32–33, y muestra un alto grado de similitud con dToll sobre la secuencia entera (aa). La secuencia de TLR4 codifica una proteína de 839 (aa) con 22 regiones LRR N–terminales y un peso molecular calculado de 90 kDa. TLR4 se relaciona más estrechamente con TLR1 y TLR6, cada uno, con 25% en total de similitud de secuencia (aa).

In vivo, el ARNm de TLR4 se expresa como una sola transcripción, y se halla en los niveles más altos en el bazo y PBL. De las poblaciones de PBL, TLR4

es expresado por células B, células dendríticas, monocitos, macrófagos, granulocitos y células T. TLR4 además es expresado en células mielomonocíticas, y presenta mayores niveles en células mononucleares. *In vitro*, el ARNm de TLR4 y la expresión de proteína son regulados en forma ascendente en células THP–1 con la diferenciación inducida por PMA. TLR4 es moderadamente regulado en forma ascendente por IFN–γ autocrino, IL–1β. La expresión de ARNm de TLR4 en células THP–1 no es afectada por la exposición a bacterias Gram positivas y bacterias Gram negativas. *Ex vivo*, la expresión de TLR4 de granulocitos y monocitos es regulada en forma ascendente con la exposición a bacterias Gram–negativas.

TLR4 forma un homodímero y requiere la asociación extracelular de un componente adicional, MD–2. Si bien los complejos de TLR2 pueden reconocer lipopolisacárido (LPS), TLR4, en general, es considerado el receptor de LPS. Sin embargo, los homodímeros de TLR4 asociados con MD–2 no se unen a LPS directamente. LPS debe primero ser ligado por la proteína de unión de LPS soluble (LBP). LBP es luego ligada ya sea por CD14 ligada a GPI, ya sea soluble. Otros componentes dependientes del tipo celular necesarios para la detección de LPS por TLR4 abarcan CXCR4, GDF–5, CD55, diversas proteínas de choque de calor (HSP, por sus siglas en inglés), y receptores de complemento (CR, por sus siglas en inglés). El complejo de TLR4 además reconoce pocos otros PAMP bacterianos, entre ellos, LTA. Además, el complejo de TLR4 reconoce virus que incluyen el virus sincitial respiratorio (RSV), el virus de la hepatitis C (HCV) y el virus de tumor mamario del ratón (MMTV). El complejo de TLR4 también puede reconocer ligandos endógenos, por ejemplo, proteínas de choque de calor (HSP60 y HSP70), fibrinógeno, dominio A de fibronectina, oligosacáridos de ácido hialurónico, heparano sulfato, proteína A surfactante (SP–A) y β–defensinas. TLR4, asimismo, forma heterodímeros tanto con TLR5, que mejora su actividad,

como con TLR1, que inhibe su actividad.

Receptor de tipo Toll 5 (TLR5).

TLR5 es cartografiado en el cromosoma 1q41–42, y el gen codifica una proteína putativa de 858 (aa) con un peso molecular calculado de 91 kDa. Se relaciona más estrechamente con TLR3, con 26% en total de identidad de secuencia (aa).

In vivo, el ARNm de TLR5 es expresado como una sola transcripción en el ovario, la próstata y PBL. TLR5 es expresado por varias poblaciones de PBL, donde la más alta expresión se halla en monocitos. TLR5 además es expresado en el costado basolateral de células epiteliales intestinales y células endoteliales intestinales del compartimiento subepitelial. *In vitro*, TLR5 es regulado en forma ascendente en células THP–1 diferenciadas por PMA, por IL–6 autocrino, IL–10 y TNF–α, si bien también es elevado por IFN–γβ. La expresión de ARNm de TLR5 es elevada luego de la exposición tanto a bacterias Gram–positivas como Gram–negativas. *Ex vivo*, la expresión de TLR5 de granulocitos y monocitos es regulada en forma descendente con la exposición a bacterias Gram–negativas. TLR5 forma un homodímero, al igual que un heterodímero, con TLR4. Ambos complejos funcionan para reconocer la proteína flagelina de bacterias flageladas. La expresión de TLR5 humano en células CHO confiere respuesta a flagelina, un constituyente monómero de flagelos bacterianos. La flagelina activa células epiteliales pulmonares para inducir la producción de citoquinas inflamatorias. Un polimorfismo de codón de detención en TLR5 se ha asociado con la sensibilidad a la neumonía causada por la bacteria flagelada *Legionella pneumophila.*

Receptor de tipo Toll 6 (TLR6).

TLR6 es cartografiado en el cromosoma 4p14, y la secuencia de TLR6 codifica una proteína de 796 (aa) que contiene 20 motivos LRR N–terminales con un peso molecular calculado de 91 kDa. TLR6 es se relaciona más estrechamente

con TLR1, TLR10 y TLR2, con 68%, 46% y 31% en total de identidad de secuencia (aa), respectivamente.

In vivo, la transcripción de TLR6 se observa en el timo, el bazo y el pulmón. La expresión de ARNm de TLR6 es más alta en células B y en monocitos. *In vitro*, la expresión de ARNm de TLR6 es regulada en forma ascendente en células THP–1 con la diferenciación inducida por PMA. TLR6 es moderadamente regulado en forma ascendente por IFN–γ autocrino, IL–1β. Sin embargo, la expresión de ARNm de TLR6 en células THP–1 no es afectada por la exposición tanto a bacterias Gram–positivas como Gram–negativas. *Ex vivo*, la expresión de TLR6 de monocitos y granulocitos es regulada en forma descendente con la exposición a bacterias Gram–negativas. TLR6 forma un heterodímero con TLR2. Como TLR1, se cree que TLR6 mejora específicamente la sensibilidad de PAMP de TLR2, y contribuye a sus capacidades de señalización a través de la heterodimerización.

Receptor de tipo Toll 7 (TLR7).

TLR7 es cartografiado en el cromosoma humano Xp22, y la secuencia de TLR7 codifica una proteína de 1049 (aa) que contiene 27 LRR N–terminales con un peso molecular calculado de 121 kDa. TLR7 se relaciona más estrechamente con TLR8 y TLR9, con 43% y 36% en total de identidad de secuencial (aa), respectivamente.

In vivo, el ARNm de TLR7 es expresado en el pulmón, la placenta, el bazo, los nódulos linfáticos y las amígdalas. La expresión de ARNm de TLR7 es más alta en monocitos, células B y células dendríticas plasmocitoideas. *In vitro*, la expresión de ARNm de TLR7 es regulada en forma ascendente en células THP–1 con la diferenciación inducida por PMA. TLR7 es altamente regulado en forma ascendente por la exposición a IL–6 y, a un alcance levemente menor, por IFN–γ autocrino, IL–1β. La expresión de ARNm de TLR7 en células THP–1 es elevada

luego de la exposición tanto a bacterias Gram–positivas como Gram–negativas. *Ex vivo*, la expresión de TLR7 es elevada luego de la exposición tanto a bacterias Gram–positivas como Gram–negativas en monocitos, y a un grado mayor, en granulocitos. TLR7 es expresado en el endosoma. La función de TLR7 consiste en la detección de la presencia de ARN de hebra simple "extraño" dentro de una célula, como una manera de responder a la invasión viral. TLR7 es una proteína estructuralmente altamente conservada, que reconoce ARN de hebra simple, rica en uridina o guanosina (ARNss) de virus tales como el virus de inmunodeficiencia humana, el virus de estomatitis vesicular y el virus de la gripe.

Receptor de tipo Toll 8 (TLR8).

TLR8 es cartografiado en el cromosoma Xp22, y la secuencia TLR8 codifica una proteína de 1041 (aa) que contiene 26 LRR N–terminales, con un peso molecular calculado de 120 kDa. TLR8 se relaciona más estrechamente con TLR7 y TLR9, con 43% y 35% en total de identidad de secuencia (aa), respectivamente.

In vivo, el ARNm de TLR8 es expresado en el pulmón, la placenta, el bazo, los nodos linfáticos, la médula ósea y PBL, donde la más alta expresión se encuentra en células de origen mieloide, tales como monocitos, granulocitos y células dendríticas mieloides. *In vitro*, la expresión de ARNm de TLR8 es regulada en forma ascendente en células THP–1 con la diferenciación inducida por PMA. TLR8 es altamente regulado en forma ascendente por IL–1β autocrino, IL–6, IL–10 y TNF–α, y es aún mayor por la exposición a IFN–γ. La expresión de ARNm de TLR8 en células THP–1 es elevada luego de la exposición tanto a bacterias Gram–positivas como Gram–negativas. *Ex vivo*, la expresión de TLR8 de monocitos incrementa mientras que la expresión de granulocitos disminuye con la exposición a bacterias Gram–negativas. TLR8 es expresado en el endosoma. La función de TLR8 consiste en la detección de la presencia de ARN de hebra simple

"extraño" dentro de una célula, como un medio para responder a la invasión viral. TLR8 es una proteína estructuralmente altamente conservada que reconoce ARN de hebra simple rica en uridina o guanosina (ARNss) de virus tales como el virus de inmunodeficiencia humana, el virus de estomatitis vesicular y el virus de la gripe.

Receptor de tipo Toll 9 (TLR9).

TLR9 es cartografiado en el cromosoma 3p21, y la secuencia de TLR9 codifica una proteína de 1032 (aa) que contiene 27 LRR N–terminales con un peso molecular calculado de 116 kDa. TLR9 se relaciona más estrechamente con TLR7 y TLR8, con 36% y 35% en total de identidad de secuencia (aa), respectivamente.

In vivo, el ARNm de TLR9 es expresado en el bazo, los nodos linfáticos, la médula ósea y PBL. Específicamente, el ARNm de TLR9 es expresado en los más altos niveles en células B y en células dendríticas. *In vitro*, TLR9 es moderadamente regulado en forma ascendente por IFN–γ autocrino, IL–1ß, IL–6, IL–10 y TNF–α en células THP–1 diferenciadas por PMA. La expresión de ARNm de TLR9 en células THP–1 no es afectada por la exposición tanto a bacterias Gram–positivas como Gram–negativas. *Ex vivo*, la expresión de TLR9 en monocitos y, en particular, en granulocitos, es regulada en forma descendente en respuesta a bacterias Gram–negativas. TLR9 forma un homodímero y reconoce ADN bacteriano no metilado. TLR9 participa en la respuesta inflamatoria a ADN bacteriano y oligonucleótidos que contienen secuencias de ADN de CpG no metilado. TLR9 se ubica internamente, tal vez, en compartimientos lisosómicos o endocíticos, donde, más probablemente encuentre PAMP que incluyen secuencias de ADN CpG no metilado.

TLR9 es un receptor para ADN CpG, y reconoce ADN CpG bacteriano y viral. EL ADN bacteriano y viral contiene motivos CpG no metilados que confieren

su actividad inmunomoduladora. En vertebrados, la frecuencia de motivos CpG es reducida en gran medida, y los residuos de citosina de motivos CpG son altamente metilados, para conducir a la anulación de la actividad inmunoestimulante. Estructuralmente, hay por lo menos dos tipos de ADN CpG: ADN CpG tipo B/K es un potente inductor de citoquinas inflamatorias tales como IL–12 y TNF–α; ADN CpG tipo A/D tiene mayor capacidad para inducir la producción de IFN–α a partir de células dendríticas plasmacitoideas (PDC, por sus siglas en inglés). TLR9 también participa en la patogénesis de trastornos autoinmunitarios, y puede ser importante en el hipertiroidismo autoinmunitario de Grave y en la producción de factor reumatoideo por células B autorreactivas. Asimismo, la internalización por el receptor Fc puede causar la inducción de PDC mediada por TLR9 de IFN–α por complejos inmunitarios que contienen IgG y cromatina, que están implicadas en la patogénesis del lupus eritematoso sistémico (SLE, por sus siglas en inglés). TLR9 participa en la patogénesis de varias enfermedades autoinmunitarias a través del reconocimiento de la estructura de cromatina.

Receptor de tipo Toll 10 (TLR10).

La secuencia de TLR10 codifica una proteína putativa de 811 (aa) con un peso molecular de 95 kDa. TLR10 se relaciona más estrechamente con TLR1 y TLR6, con 48% y 46% en total de identidad (aa), respectivamente.

In vivo, la expresión de ARNm de TLR10 es más alta en tejidos relacionados con el sistema inmunológico que incluyen el bazo, los nodos linfáticos, el timo y las amígdalas. El ARNm de TLR10 es expresado más altamente en células B y en células dendríticas plasmacitoideas (PDC). *In vitro*, TLR10 es moderadamente regulado en forma ascendente por IFN–γ autocrino, IL–1β, IL–6, IL–10 y TNF–α en células THP–1 diferenciadas por PMA. La expresión de ARNm de TLR10 en células THP–1 es elevada luego de la

exposición tanto a bacterias Gram–positivas como Gram–negativas. *Ex vivo*, la expresión de TLR10 de monocitos aumenta, mientras que la expresión de granulocitos disminuye con la exposición a bacterias Gram–negativas.

Receptor de tipo Toll 11 (TLR11).

TLR11 es expresado en células epiteliales de la vejiga, y media la resistencia a la infección por bacterias uropatógenas en el ratón.

Como se presenta con anterioridad, TLR2 y TLR4 reconocen productos de la pared celular bacteriana de bacterias Gram–positivas y Gram–negativas, respectivamente. TLR5 reconoce un epítopo estructural de flagelina bacteriana; TLR3, TLR7, TLR8 y TLR9 reconocen diferentes formas de ácido nucleico derivado de microbios.

Los dominios TIR interactúan con varias moléculas adaptadoras que contienen dominios TIR (MyD88), proteína adaptadora que contiene dominio TIR (TIRAP), IFN–β inductor de adaptador que contiene dominio TIR (TRIF), y molécula adaptadora relacionada con TRIF (TRAM), que activan una cascada de eventos que logran la inducción del factor de transcripción..

Vías de señalización de TLR.

Los TLR se distribuyen a través de la célula. TLR1, TLR2, TLR3 y TLR4 son expresados sobre la superficie celular, mientras que TLR3, TLR7, TLR8 y TLR9 son expresados en compartimientos intracelulares tales como los endosomas. El reconocimiento mediado por TLR3, TLR7 o TLR9 de sus ligandos requiere la mutación endosómica y el procesamiento. Cuando los macrófagos, monocitos, las células dendríticas o las células no inmunitarias que se tornan células que presentan antígeno rodean bacterias por fagocitosis, las bacterias se degradan, y se libera ADN CpG en fagosomas–lisosomas o en endosomas–lisosomas, donde estas pueden interactuar con TLR9 que ha sido reclutado desde el retículo endoplasmático con la absorción no específica de ADN CpG. Además,

cuando los virus invaden células por endocitosis mediada por receptores, los contenidos virales son expuestos al citoplasma por la fusión de la membrana viral con la membrana endosómica. Esto logra la exposición de ligandos de TLR tales como ARNds, ARNss y ADN CpG a TLR9 en los compartimientos fagosómico/lisosómico, o endosómico/lisosómico.

En las vías de señalización corriente descendente del dominio TIR, un adaptador que contiene dominio TIR, MyD88, es esencial para la inducción de citoquinas inflamatorias tales como TNF–α e IL–12 a través de todos los TLR. Si bien las moléculas adaptadoras que contienen dominio TIR (MyD88) son comunes a todos los TLR, las vías de señalización de TLR individuales son divergentes, y la activación de TLR específicos conduce a patrones levemente diferentes de perfiles de expresión de genes. Solo a modo de ejemplo, la activación de las vías de señalización de TLR3 y TLR4 logra la inducción de interferones de tipo I (IFN), mientras que la activación de las vías mediadas por TLR2 y TLR5 no lo hacen. Sin embargo, la activación de las vías de señalización de TLR7, TLR8 y TLR9 también conduce a la inducción de IFN de Tipo I, si bien esto se produce a través de mecanismos distintos de la inducción mediada por TLR3/4.

Una vez ligados, los TLR inician una cascada de transducción de señales que conduce a la activación de NFκB mediante el gen 88 de respuesta primaria a la diferenciación mieloide de proteína adaptadora (MyD88) y el reclutamiento de la quinasa asociada con receptor IL–1 (IRAK, por sus siglas en inglés). La vía dependiente de MyD88 es análoga a la señalización por los receptores IL–1, y se considera que MyD88, que alberga un dominio TIR C–terminal y un dominio de muerte N–terminal, se asocia con el dominio TIR de TLR. Con la estimulación, MyD88 recluta IRAK–4 hacia los TLR a través de la interacción de los dominios de muerte de ambas moléculas, y facilita la fosforilación mediada por IRAK–4 de

IRAK–1. La fosforilación de IRAK–1 luego conduce al reclutamiento del factor 6 asociado con el receptor de TNF (TRAF6, por sus siglas en inglés), lo que conduce a la activación de dos vías de señalización distintas. Una vía conduce a la activación de factores de transcripción AP–1 a través de la activación de MAP quinasas. Otra vía activa el complejo TAK1/TAB, que mejora la actividad del complejo IκB quinasa (IKK). Una vez activado, el complejo IKK induce la fosforilación y la posterior degradación del inhibidor de NFκB IκB, que conduce a la translocación nuclear de factor de transcripción NFκB y la iniciación de la transcripción de genes cuyos promotores contienen sitios de unión de NFκB, tales como citoquinas. La vía dependiente de MyD88 cumple un rol crucial, y es esencial para la producción de citoquinas inflamatorias a través de todos los TLR.

La estimulación de células que expresan TLR8, tales como PBMC, logra la producción de altos niveles de IL–12, IFN–γ, IL–1, TNF–α, IL–6 y otras citoquinas inflamatorias. Asimismo, la estimulación de células que expresan TLR7, tales como células dendríticas plasmacitoideas, logra la producción de altos niveles de interferón–α (IFNα) y bajos niveles de citoquinas inflamatorias. En consecuencia, a través de la activación de células dendríticas y otras células que presentan antígeno, se espera que la unión de TLR7, TLR8 o TLR9 y la producción de citoquina activen diversos mecanismos de respuesta inmunitaria adquirida que conducen a la destrucción de patógenos, células infectadas o células tumorales.

Los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, las composiciones farmacéuticas y combinaciones que se proveen en la presente solicitud son útiles como moduladores de la actividad de receptores tipo toll, y se usan en el tratamiento de una amplia variedad de enfermedades o trastornos asociados con dichos receptores. En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus

isómeros, y las composiciones farmacéuticas que se proveen en esta solicitud son moduladores de la actividad de TLR7, y son útiles en el tratamiento de enfermedades o trastornos asociados con TLR7. En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, y las composiciones farmacéuticas que se proveen en esta solicitud son agonistas de la actividad de TLR7, y son útiles en el tratamiento de enfermedades o trastornos asociados con TLR7. En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, y las composiciones farmacéuticas que se proveen en esta solicitud son moduladores de la actividad de TLR8, y son útiles en el tratamiento de enfermedades o trastornos asociados con TLR8. En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, y las composiciones farmacéuticas que se proveen en esta solicitud son agonistas de la actividad de TLR8, y son útiles en el tratamiento de enfermedades o trastornos asociados con TLR8.

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, las composiciones farmacéuticas y combinaciones que se proveen en esta solicitud se usan en el tratamiento de enfermedades o trastornos respiratorios que incluyen, sin limitación, asma, asma bronquial, asma alérgica, asma intrínseca, asma extrínseca, asma inducida por el ejercicio, asma inducida por fármacos (que incluyen aspirina y la inducida por AINE) y asma inducida por el polvo, enfermedad pulmonar obstructiva crónica (EPOC); bronquitis, que incluye bronquitis infecciosa y eosinófila; enfisema, bronquiectasia; fibrosis quística; sarcoidosis; pulmón del productor agrícola y enfermedades relacionadas;

neumonitis de hipersensibilidad; fibrosis pulmonar, que incluye alveolitis fibrosante criptógena, neumonías intersticiales idiopáticas, fibrosis con complicación de terapia antineoplásica, e infección crónica, que incluye tuberculosis y aspergilosis y otras infecciones fúngicas; complicaciones del trasplante pulmonar; trastornos vasculíticos y trombóticos de la vasculatura pulmonar, e hipertensión pulmonar; actividad antitusiva que incluye el tratamiento de tos crónica asociada con afecciones inflamatorias y de secreción de las vías respiratorias; y tos iatrogénica; rinitis aguda y crónica que incluye rinitis medicamentosa y rinitis vasomotora; rinitis alérgica y estacional que incluye rinitis nerviosa (fiebre del heno); poliposis nasal; infección viral aguda que incluye resfrío común e infección debida al virus sincitial respiratorio, gripe, coronavirus (que incluye SARS) y adenovirus.

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, las composiciones farmacéuticas y las combinaciones que se proveen en esta solicitud se usan en el tratamiento de trastornos dermatológicos, que incluyen, sin limitación, psoriasis, dermatitis atópica, dermatitis de contacto u otras dermatosis eccematosas, y reacciones de hipersensibilidad de tipo demorada; fito– y fotodermatitis; dermatitis seborreica, dermatitis herpetiforme, liquen plano, liquen escleroatrófico, piodermia gangrenosa, sarcoide de la piel, carcinoma de célula basal, queratosis actínica, lupus eritematoso discoide, pénfigo, penfigoide, epidermólisis vesicular, urticaria, angioedema, vasculitis, eritemas tóxicos, eosinofilias cutáneas, alopecia sonata, calvicie de patrón masculino, síndrome de Sweet, síndrome de Weber–Christian, eritema multiforme; celulitis, tanto infecciosa como no infecciosa; paniculitis; linfomas cutáneos, cáncer de piel de tipo no–melanoma y otras lesiones displásicas; trastornos inducidos por fármacos que incluyen erupciones por fármacos fijos.

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales

aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, las composiciones farmacéuticas y las combinaciones que se proveen en esta solicitud se usan en el tratamiento de enfermedades o trastornos oculares que incluyen, sin limitación, blefaritis, conjuntivitis, que incluye conjuntivitis alérgica y primaveral; iritis; uveítis anterior y posterior; coroiditis; trastornos inflamatorios autoinmunitarios, degenerativos o inflamatorios que afectan la retina; oftalmitis, que incluye oftalmitis sintomática; sarcoidosis; infecciones que incluyen infecciones virales, fúngicas y bacterianas.

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, las composiciones farmacéuticas y las combinaciones que se proveen en esta solicitud se usan en el tratamiento de enfermedades o trastornos genitourinarios que incluyen, sin limitación, nefritis, que incluye nefritis intersticial y glomerulonefritis; síndrome nefrótico; cistitis, que incluye cistitis aguda y crónica (intersticial) y úlcera de Hunner; uretritis aguda y crónica, prostatitis, epididimitis, ooforitis y salpingitis; vulvovaginitis; enfermedad de Peyronie; disfunción eréctil (tanto masculina como femenina).

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, las composiciones farmacéuticas y las combinaciones que se proveen en esta solicitud se usan en el tratamiento de rechazo de aloinjertos, que incluye, sin limitación, rechazo agudo y crónico luego de, por ejemplo, el trasplante de riñón, corazón, hígado, pulmón, médula ósea, piel o córnea, o luego de la transfusión de sangre; o la enfermedad crónica de injerto contra huésped.

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, las composiciones farmacéuticas y las combinaciones que se proveen

en esta solicitud se usan en el tratamiento de otros trastornos autoinmunitarios y alérgicos que incluyen, sin limitación, artritis reumatoide, síndrome de intestino irritable, lupus eritematoso sistémico, esclerosis múltiple, tiroiditis de Hashimoto, enfermedad de Crohn, enfermedad intestinal inflamatoria (IBD, por sus siglas en inglés), enfermedad de Grave, enfermedad de Addison, diabetes sacarina, purpura trombocitopénica idiopática, fascitis eosinófia, síndrome de hiper–IgE, síndrome antifosfolipídico y síndrome de Sazary.

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, y las composiciones farmacéuticas que se proveen en esta solicitud se usan en el tratamiento de cáncer, que incluye, sin limitación, tumores y enfermedades malignas de próstata, mama, pulmón, ovario, páncreas, intestino y colon, estómago, piel y cerebro, que afectan los sistemas de la médula ósea (que incluye leucemias) y linfoproliferativo, por ejemplo, linfoma de Hodgkin y no hodgkiniano; que incluye la prevención y el tratamiento de recurrencias tumorales y enfermedad metastásica, y síndromes paraneoplásicos. En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, y las composiciones farmacéuticas que se proveen en esta solicitud son útiles como moduladores de la actividad de receptores tipo toll, y se usan en el tratamiento de neoplasias que incluyen, sin limitación, carcinoma de célula basal, carcinoma de célula escamosa, queratosis actínica, melanoma, carcinomas, sarcomas, leucemias, carcinoma de célula renal, sarcoma de Kaposi, leucemia mielógena, leucemia linfocítica crónica y mieloma múltiple.

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, las composiciones farmacéuticas y las combinaciones que se proveen

en esta solicitud se usan en el tratamiento de enfermedades infecciosas que incluyen, sin limitación, enfermedades virales tales como verrugas genitales, verrugas comunes, verrugas plantares, virus sincitial respiratorio (RSV), hepatitis B, hepatitis C, virus del dengue, virus de herpes simple (solo a modo de ejemplo, HSV–I, HSV–II, CMV o VZV), molusco contagioso, vacuna, viruela, lentivirus, virus de inmunodeficiencia humana (HIV), virus de papiloma humano (HPV), citomegalovirus (CMV), virus de varicela zoster (VZV), rinovirus, enterovirus, adenovirus, coronavirus (por ejemplo, SARS), gripe, paragripe, virus de la paperas, virus del sarampión, papovavirus, hepadnavirus, flavivirus, retrovirus, arenavirus (solo a modo de ejemplo, LCM, virus de Junin, virus de Machupo, virus de Guanarito y fiebre de Lassa) y filovirus (solo a modo de ejemplo, virus del ébola o virus de Marburgo).

En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, las composiciones farmacéuticas y las combinaciones que se proveen en esta solicitud se usan en el tratamiento de infecciones bacterianas, fúngicas y protozoales que incluyen, sin limitación, tuberculosis e infección por *micobacterium avium*, lepra; neumocistosis carnii, criptosporidiosis, histoplasmosis, toxoplasmosis, infección por tripanosoma, leishmaniosis, infecciones causadas por bacterias de los géneros *Escherichia*, *Enterobacter, Salmonella, Staphylococcus, Klebsiella, Proteus, Pseudomonas, Streptococcus* y *Chlamydia*, e infecciones fúngicas tales como candidiasis, aspergilosis, histoplasmosis, meningitis criptocócica.

En ciertas realizaciones, los compuestos de las Fórmulas (I) y (I–A), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros se usan como potenciadores inmunitarios. En ciertas realizaciones, los compuestos que se proveen en esta solicitud se incluyen en composiciones

inmunógenas o se usan en combinación con composiciones inmunógenas. En ciertas realizaciones, las composiciones inmunógenas son útiles como vacunas, y el compuesto se presenta en una cantidad suficiente para mejorar una respuesta inmunitaria a la vacuna, o a un antígeno en mezcla con el compuesto. La vacuna comprende por lo menos un antígeno, que puede ser un antígeno bacteriano o un antígeno asociado con cáncer, o un antígeno viral. En ciertas realizaciones, el compuesto de la Fórmula (I) o (I–A), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, y las composiciones farmacéuticas que se proveen en esta solicitud se incluyen en vacunas terapéuticas o se usan en combinación con vacunas terapéuticas. En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, y las composiciones farmacéuticas que se proveen en esta solicitud se incluyen en vacunas profilácticas o se usan en combinación con vacunas profilácticas. En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, y las composiciones farmacéuticas que se proveen en esta solicitud se incluyen en vacunas virales terapéuticas, o se usan en combinación con estas. En ciertas realizaciones, los compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros, y las composiciones farmacéuticas que se proveen en esta solicitud se incluyen en vacunas oncológicas, o se usan en combinación con estas.

En otras realizaciones, los compuestos de la Fórmula (I), o una de sus sales aceptables para uso farmacéutico, que se describen en esta solicitud, son útiles para el tratamiento de la piel dañada o envejecida, tal como cicatrices y arrugas.

Administración y composiciones farmacéuticas.

Para los usos terapéuticos de los compuestos de la Fórmula (I), o sus sales aceptables para uso farmacéutico, solvatos, N–óxidos, profármacos y sus isómeros que aquí se describen, dichos compuestos se administran en cantidades terapéuticamente eficaces, ya sea solos, ya sea como parte de una composición farmacéutica. En consecuencia, se proveen en la presente solicitud composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula (I), como se describe en la presente solicitud, sus sales aceptables para uso farmacéutico o sus solvatos, y uno o más portadores, diluyentes o excipientes aceptables para uso farmacéutico. Además, dichos compuestos y composiciones se administran en forma individual o en combinación con uno o más agentes terapéuticos adicionales. El método de administración de dichos compuestos y composiciones comprende, sin limitación, la administración oral, administración rectal, administración parenteral, administración intravenosa, administración intravítrea, administración intramuscular, inhalación, administración intranasal, administración tópica, administración oftálmica o administración ótica.

La cantidad terapéuticamente eficaz variará conforme a, entre otros factores, la enfermedad indicada, la gravedad de la enfermedad, la edad y la salud relativa del sujeto, la potencia del compuesto administrado, el modo de administración y el tratamiento deseado. En ciertas realizaciones, en términos de la dosificación diaria de un compuesto de la Fórmula (I), se indica el logro de resultados satisfactorios sistémicamente con dosificaciones diarias de aproximadamente 0,03 a 2,5 mg/kg por peso corporal. En ciertas realizaciones, la dosificación diaria de un compuesto de la Fórmula (I), administrado por inhalación, se encuentra en el rango de 0,05 microgramos por kilogramo de peso corporal (µg/kg) a 100 microgramos por kilogramo de peso corporal (µg/kg). En otras realizaciones, la dosificación diaria de un compuesto de la Fórmula (I),

administrado por vía oral, se encuentra en el rango de 0,01 microgramos por kilogramo de peso corporal (µg/kg) a 100 miligramos por kilogramo de peso corporal (mg/kg). Una dosificación diaria indicada en mamíferos mayores, por ejemplo, en seres humanos, se encuentra en el rango de aproximadamente 0,5 mg a aproximadamente 100 mg de un compuesto de la Fórmula (I), de modo conveniente, administrado, por ejemplo, en dosis divididas de hasta cuatro veces por día, o en forma de liberación controlada. En ciertas realizaciones, las formas farmacéuticas unitarias para administración oral comprenden de alrededor de 1 a 50 mg de un compuesto de la Fórmula (I).

Otros aspectos proporcionados en la presente solicitud comprenden procesos para la preparación de composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula (I) descripto en esta solicitud, o sus sales aceptables para uso farmacéutico o sus solvatos. En ciertas realizaciones, dichos procesos incluyen la mezcla de un compuesto de la Fórmula (I) descripto en esta solicitud y sus sales aceptables para uso farmacéutico, con uno o más portadores, diluyentes o excipientes farmacéuticamente aceptables. En ciertas realizaciones, las composiciones farmacéuticas que comprenden un compuesto de la Fórmula (I) en forma libre o en forma de un solvato o una sal aceptable para uso farmacéutico, junto con por lo menos un portador, diluyente o excipiente farmacéuticamente aceptable, se elaboran por medio de métodos de mezcla, granulación o revestimiento. En otras realizaciones, dichas composiciones contienen, opcionalmente, excipientes tales como agentes conservantes, estabilizadores, humectantes o emulsionantes, promotores de la solución, sales para la regulación de la presión osmótica y reguladores. En otras realizaciones, dichas composiciones son esterilizadas.

Formas farmacéuticas orales.

En ciertas realizaciones, las composiciones farmacéuticas que contienen por lo menos un compuesto de la Fórmula (I) se administran por vía oral como formas farmacéuticas separadas, donde dichas formas farmacéuticas incluyen, sin limitación, cápsulas, cápsulas de gelatina, comprimidos en forma de cápsulas, comprimidos, comprimidos masticables, polvos, gránulos, jarabes, jarabes saborizados, soluciones o suspensiones en líquidos acuosos o no acuosos, batidos o espumas comestibles y emulsiones líquidas de aceite en agua o emulsiones líquidas de agua en aceite.

Las cápsulas, cápsulas de gelatina, comprimidos en forma de cápsulas, comprimidos, comprimidos masticables, los polvos o gránulos, utilizados para la administración oral de por lo menos un compuesto de la Fórmula (I), se preparan por medio de la mezcla de por lo menos un compuesto de la Fórmula (I) (ingrediente activo) junto con por lo menos un excipiente, usando técnicas de composición farmacéutica convencionales. Ejemplos no limitativos de excipientes utilizados en formas farmacéuticas orales descriptas en esta solicitud incluyen, sin limitación, aglutinantes, rellenos, desintegrantes, lubricantes, absorbentes, colorantes, saborizantes, conservantes y edulcorantes.

Ejemplos no limitativos de dichos aglutinantes incluyen, entre otros, almidón de maíz, almidón de papa, pasta de almidón, almidón pregelatinizado u otros almidones, azúcares, gelatina, gomas naturales y sintéticas tales como goma de acacia, alginato sódico, ácido algínico, otros alginatos, goma de tragacanto, goma de guar, celulosa y sus derivados (solo a modo de ejemplo, etilcelulosa, acetato de celulosa, carboximetilcelulosa de calcio, carboximetilcelulosa de sodio, metilcelulosa, hidroxipropilmetilcelulosa y celulosa microcristalina), silicato de magnesio aluminio, polivinilpirrolidona y sus combinaciones.

Ejemplos no limitativos de dichos rellenos comprenden, entre otros, talco, carbonato de calcio (por ejemplo, gránulos o polvo), celulosa microcristalina, celulosa en polvo, dextratos, caolín, manitol, ácido silícico, sorbitol, almidón, almidón pregelatinizado, y sus mezclas. En ciertas realizaciones, el aglutinante o el relleno en las composiciones farmacéuticas que se proveen en esta solicitud se presenta en una cantidad de aproximadamente 50 a aproximadamente 90 por ciento en peso de la composición farmacéutica o forma farmacéutica.

Ejemplos no limitativos de dichos agentes desintegrantes comprende, entre otros, agar–agar, ácido algínico, alginato de sodio, carbonato de calcio, carbonato de sodio, celulosa microcristalina, croscarmelosa sódica, crospovidona, polacrilina de potasio, glicolato de almidón sódico, almidón de papa o tapioca, almidón pregelatinizado, otros almidones, arcillas, otras alginas, otras celulosas, gomas y sus combinaciones. En ciertas realizaciones, la cantidad de desintegrante utilizada en las composiciones farmacéuticas que se proveen en la presente solicitud es de aproximadamente 0,5 a aproximadamente 15 por ciento en peso de desintegrante, si bien, en otras realizaciones, la cantidad es de alrededor de 1 a alrededor de 5 por ciento en peso de desintegrante.

Ejemplos no limitativos de dichos lubricantes incluyen, entre otros, estearato de sodio, estearato de calcio, estearato de magnesio, ácido esteárico, aceite mineral, aceite mineral liviano, glicerol, sorbitol, manitol, polietilenglicol, otros glicoles, lauril sulfato de sodio, talco, aceite vegetal hidrogenado (solo a modo de ejemplo, aceite de maní, aceite de semilla de algodón, aceite de girasol, aceite de sésamo, aceite de oliva, aceite de maíz y aceite de soja), estearato de zinc, oleato de sodio, oleato de etilo, laureato de etilo, agar, sílice, un gel de sílice siloide (AEROSIL 200, fabricado por W. R. Grace Co. de Baltimore, Md.), un aerosol coagulado de sílice sintética (comercializado por Degussa Co. de Plano, Tex.), CAB–O–SIL (un producto de dióxido de silicio pirogeno comercializado por

Cabot Co. de Boston, Mass.) y sus combinaciones. En ciertas realizaciones, la cantidad de lubricantes utilizados en las composiciones farmacéuticas que se proveen en la presente solicitud es aquella cantidad inferior a aproximadamente 1 por ciento en peso de las composiciones farmacéuticas o formas farmacéuticas.

Ejemplos no limitativos de dichos diluyentes comprenden, entre otros, lactosa, dextrosa, sacarosa, manitol, sorbitol, celulosa, glicina o sus combinaciones.

En ciertas realizaciones, los comprimidos y las cápsulas se preparan mediante la mezcla uniforme de por lo menos un compuesto de la Fórmula (I) (ingredientes activos) con portadores líquidos, portadores sólidos finamente divididos, o ambos, y luego, si es necesario, la forma del producto en la presentación deseada. En ciertas realizaciones, los comprimidos se preparan mediante la compresión. En otras realizaciones, los comprimidos se preparan mediante el moldeado.

En ciertas realizaciones, por lo menos un compuesto de la Fórmula (I) se administra por vía oral como una forma farmacéutica de liberación controlada. Dichas formas farmacéuticas se usan para proporcionar la liberación lenta o controlada de uno o más compuestos de la Fórmula (I). La liberación controlada se logra usando, por ejemplo, hidroxipropilmetil celulosa y otras matrices poliméricas, geles, membranas permeables, sistemas osmóticos, revestimientos de múltiples capas, micropartículas, liposomas, microesferas o una combinación de los anteriores. En ciertas realizaciones, las formas farmacéuticas de liberación controlada se usan para extender la actividad del compuesto de la Fórmula (I), reducir la frecuencia de la dosificación e incrementar el cumplimiento del paciente con el tratamiento.

Las administraciones de los compuestos de la Fórmula (I) como líquidos orales, tales como soluciones, jarabes y elíxires, se preparan en formas

farmacéuticas unitarias, de modo que la cantidad determinada de soluciones, jarabes o elíxires contiene una cantidad predeterminada de un compuesto de la Fórmula (I). Los jarabes se preparan mediante la disolución del compuesto en una solución acuosa adecuadamente saborizada, mientras que los elíxires se preparan a través del uso de vehículo alcohólico no tóxico. Las suspensiones se formulan mediante la dispersión del compuesto en un vehículo no tóxico. Ejemplos no limitativos de excipientes utilizados en líquidos orales para la administración oral incluyen, entre otros, solubilizadores, emulsionantes, agentes saborizantes, conservantes y agentes colorantes. Ejemplos no limitativos de solubilizadores y emulsionantes incluyen, entre otros, agua, glicoles, aceites, alcoholes, alcoholes de isoestearilo etoxilados y éteres de polioxietilensorbitol. Ejemplos no limitativos de conservantes incluyen, entre otros, benzoato de sodio. Ejemplos no limitativos de agentes saborizantes comprenden, entre otros, aceite de menta piperita o edulcorantes naturales o sacarina u otros edulcorantes artificiales.

Formas farmacéuticas parenterales.

En ciertas realizaciones, las composiciones farmacéuticas que contienen por lo menos un compuesto de la Fórmula (I) se administran por vía parenteral mediante diversas vías que abarcan, sin limitación, las vías subcutánea, intravenosa (que incluye inyección de bolo), intramuscular e intraarterial.

Dichas formas farmacéuticas parenterales se administran en forma de soluciones, suspensiones, productos liofilizados o secos listos para la disolución o la suspensión en un vehículo farmacéuticamente aceptable para inyección (polvos reconstituibles) y emulsiones, todos ellos, estériles o esterilizables. Los vehículos utilizados en dichas formas farmacéuticas incluyen, sin limitación, agua para inyección USP; vehículos acuosos tales como, sin limitación, solución de cloruro de sodio, solución de cloruro sódico compuesta, solución de dextrosa, solución de

dextrosa y cloruro sódico y solución de lactato sódico compuesta; vehículos miscibles con agua, tales como, sin limitación, alcohol etílico, polietilenglicol y polipropilenglicol; y vehículos no acuosos, tales como, sin limitación, aceite de maíz, aceite de semilla de algodón, aceite de maní, aceite de sésamo, etil oleato, isopropil miristato y bencil benzoato.

Formas farmacéuticas transdérmicas.

En ciertas realizaciones, las composiciones farmacéuticas que contienen por lo menos un compuesto de la Fórmula (I) se administran por vía transdérmica. Dichas formas farmacéuticas transdérmicas incluyen parches de "tipo depósito" o "tipo matriz", que se aplican a la piel y se usan durante un período de tiempo especificado a fin de permitir la penetración de una cantidad deseada de un compuesto de la Fórmula (I). Solo a modo de ejemplo, dichos dispositivos transdérmicos se presentan en forma de una venda que comprende un miembro de soporte, un depósito que contiene el compuesto, opcionalmente, con portadores, opcionalmente, una barrera para el control de la velocidad para suministrar el compuesto a la piel del huésped a una velocidad controlada y predeterminada durante un período de tiempo prolongado, y medios para asegurar el dispositivo a la piel. En otras realizaciones, se usan las formulaciones transdérmicas de matriz.

Las formulaciones para la administración transdérmica de un compuesto de la Fórmula (I) incluyen una cantidad eficaz de un compuesto de la Fórmula (I), un portador y un diluyente opcional. Un portador comprende, sin limitación, solventes farmacológicamente aceptables absorbibles para auxiliar en el pasaje a través de la piel del huésped, por ejemplo, agua, acetona, etanol, etilenglicol, propilenglicol, butan–1,3–diol, isopropil miristato, isopropil palmitato, aceite mineral y sus combinaciones.

En ciertas realizaciones, dichos sistemas de administración transdérmica

comprenden mejoradores de la penetración para auxiliar en la administración de uno o más compuestos de la Fórmula (I) al tejido. Dichos mejoradores de la penetración incluyen, sin limitación, acetona; diversos alcoholes tales como etanol, oleílo y tetrahidrofurilo; sulfóxidos de alquilo tales como sulfóxido de dimetilo; dimetilacetamida; dimetilformamida; polietilenglicol; pirrolidonas tales como polivinilpirrolidona; grados de Kollidon (Povidona, Polividona); urea; y diversos ésteres de azúcares insolubles o solubles en agua tales como Tween 80 (polisorbato 80) y Span 60 (sorbitano monoestearato).

En otras realizaciones, el pH de dicha composición farmacéutica transdérmica o forma farmacéutica, o del tejido al cual se aplica la composición farmacéutica o la forma farmacéutica, se ajusta de manera de mejorar el suministro de uno o más compuestos de la Fórmula (I). En otras realizaciones, la polaridad de un portador solvente, su concentración iónica, o su tonicidad se ajustan de modo de mejorar el suministro. En otras realizaciones, se agregan compuestos tales como estearatos a fin de alterar convenientemente la hidrofilicidad o lipofilicidad de uno o más compuestos de la Fórmula (I), de manera de mejorar el suministro. En ciertas realizaciones, dichos estearatos sirven como un vehículo lípido para la formulación, como un agente emulsionante o surfactante, y como un agente para mejorar la penetración o para mejorar el suministro. En otras realizaciones, se usan diferentes sales, hidratos o solvatos de los compuestos de la Fórmula (I) a fin de ajustar las propiedades de la composición resultante.

Formas farmacéuticas tópicas.

En ciertas realizaciones, por lo menos un compuesto de la Fórmula (I) se administra por medio de la aplicación tópica de composición farmacéutica que contiene por lo menos un compuesto de la Fórmula (I) en forma de lociones, geles, ungüentos, soluciones, emulsiones, suspensiones o cremas. Las

formulaciones adecuadas para aplicación tópica a la piel son soluciones acuosas, ungüentos, cremas o geles, mientras que las formulaciones para administración oftálmica son soluciones acuosas. Dichas formulaciones contienen, de manera opcional, solubilizadores, estabilizadores, agentes mejoradores de la tonicidad, reguladores y conservantes.

Dichas formulaciones tópicas incluyen por lo menos un portador, y opcionalmente, por lo menos un diluyente. Dichos portadores y diluyentes incluyen, sin limitación, agua, acetona, etanol, etilenglicol, propilenglicol, butano–1,3–diol, isopropil miristato, isopropil palmitato, aceite mineral y sus combinaciones.

En ciertas realizaciones, dichas formulaciones tópicas comprenden mejoradores de la penetración para auxiliar en la administración de uno o más compuestos de la Fórmula (I) al tejido. Dichos mejoradores de la penetración incluyen, sin limitación, acetona; diversos alcoholes tales como etanol, oleílo y tetrahidrofurilo; sulfóxidos de alquilo tales como sulfóxido de dimetilo; dimetilacetamida; dimetilformamida; polietilenglicol; pirrolidonas tales como polivinilpirrolidona; grados de Kollidon (Povidona, Polividona); urea; y diversos ésteres de azúcares insolubles o solubles en agua tales como Tween 80 (polisorbato 80) y Span 60 (sorbitano monoestearato).

En ciertas realizaciones, las composiciones farmacéuticas que contienen por lo menos un compuesto de la fórmula (I) se administran por inhalación. Las formas farmacéuticas para administración por inhalación se formulan como aerosoles o polvos secos. Las formulaciones en aerosol para administración por inhalación comprenden una solución de suspensión fina de por lo menos un compuesto de la Fórmula (I) en un solvente acuoso o no acuoso farmacéuticamente aceptable. Además, dichas composiciones farmacéuticas, en forma opcional, comprenden una base de polvo tal como lactosa, glucosa,

trehalosa, manitol o almidón, y opcionalmente, un modificador del comportamiento tal como L–leucina u otro aminoácido o sales metálicas de ácido esteárico tal como estearato de calcio o magnesio.

En ciertas realizaciones, los compuestos de la Fórmula (I) se administran directamente al pulmón mediante la inhalación usando un inhalador de dosis medidas ("MDI", por sus siglas en inglés), que utiliza latas que contienen un propulsor de baja ebullición adecuado, por ejemplo, diclorodifluormetano, triclorofluormetano, diclorotetrafluoretano, dióxido de carbono u otro gas adecuado; o un dispositivo inhalador de polvo seco (DPI, por sus siglas en inglés) que utiliza un estallido de gas para crear una nube de polvo seco dentro de un recipiente, que luego es inhalada por el paciente. En ciertas realizaciones, se formulan cápsulas y cartuchos de gelatina para el uso en un inhalador o insuflador, que contienen una mezcla de polvo de un compuesto de la Fórmula (I) y una base de polvo, tal como lactosa o almidón. En ciertas realizaciones, los compuestos de la Fórmula (I) se suministran al pulmón usando un dispositivo de pulverización líquida, donde dicho dispositivo utiliza orificios de boquilla extremadamente pequeños para aerosolizar formulaciones de fármacos líquidas que luego pueden ser directamente inhaladas hacia el pulmón. En otras realizaciones, los compuestos de la Fórmula (I) se suministran al pulmón usando un dispositivo nebulizador, donde el nebulizador crea un aerosol de formulación de fármaco líquida usando energía ultrasónica para formar partículas finas que pueden ser fácilmente inhaladas. En otras realizaciones, los compuestos de la Fórmula (I) se suministran al pulmón usando un dispositivo de aerosol electrohidrodinámico ("EHD", por sus siglas en inglés), donde dichos dispositivos de aerosol EHD utilizan energía eléctrica para aerosolizar suspensiones o soluciones de fármaco líquidas.

En ciertas realizaciones, la composición farmacéutica que contiene por lo

menos un compuesto de la Fórmula (I), o sus sales aceptables para uso farmacéutico y sus solvatos, descripta en la presente solicitud, además contiene uno o más mejoradores de la absorción. En ciertas realizaciones, dichos mejoradores de la absorción incluyen, sin limitación, glicocolato de sodio, caprato de sodio, N–lauril–β–D–maltopiranosida, EDTA y micelas mezcladas.

En ciertas realizaciones, las composiciones farmacéuticas que contienen por lo menos un compuesto de la Fórmula (I) se administran por vía nasal. Las formas farmacéuticas para administración nasal se formulan como aerosoles, soluciones, gotas, geles o polvos secos.

En ciertas realizaciones, las composiciones farmacéuticas que contienen por lo menos un compuesto de la Fórmula (I) se administran por vía rectal en forma de supositorios, enemas, ungüento, cremas, espumas rectales o geles rectales. En ciertas realizaciones, dichos supositorios se preparan a partir de suspensiones o emulsiones grasas, manteca de cacao u otros glicéridos.

En ciertas realizaciones, las composiciones farmacéuticas que contienen por lo menos un compuesto de la Fórmula (I) se administran por vía oftálmica como gotas oculares. Dichas formulaciones son soluciones acuosas que contienen, opcionalmente, solubilizadores, estabilizadores, agentes mejoradores de la tonicidad, reguladores y conservantes.

En ciertas realizaciones, las composiciones farmacéuticas que contienen por lo menos un compuesto de la Fórmula (I) se administran por vía ótica como gotas para el oído. Dichas formulaciones son soluciones acuosas que, opcionalmente, contienen solubilizadores, estabilizadores, agentes mejoradores de la tonicidad, reguladores y conservantes.

En ciertas realizaciones, las composiciones farmacéuticas que contienen por lo menos un compuesto de la Fórmula (I) se formulan como una preparación de absorción lenta. Dichas formulaciones de larga acción se administran mediante

la implantación (por ejemplo, subcutánea o intramuscular), o por inyección intramuscular. En ciertas realizaciones, dichas formulaciones incluyen materiales poliméricos o hidrófobos (por ejemplo, como una emulsión en un aceite aceptable) o resinas de intercambio iónico, o son derivados escasamente solubles, por ejemplo, una sal escasamente soluble.

En la presente solicitud, se proveen compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico y sus solvatos, y composiciones farmacéuticas que contienen por lo menos un compuesto de la Fórmula (I) y sus sales aceptables para uso farmacéutico y sus solvatos, para el uso en la modulación de la actividad de TLR, y en consecuencia, para el uso en la prevención o el tratamiento de enfermedades y trastornos asociados con la actividad de TLR. En ciertas realizaciones, dichos compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico y sus solvatos y las composiciones farmacéuticas son agonistas de TLR7, y en consecuencia, se usan en el tratamiento de enfermedades y trastornos asociados con TLR7. En ciertas realizaciones, dichos compuestos de la Fórmula (I), sus sales aceptables para uso farmacéutico y sus solvatos y las composiciones farmacéuticas son agonistas de TLR8, y en consecuencia, se usan en el tratamiento de enfermedades y trastornos asociados con TLR8.

Además, se proveen en la presente solicitud métodos para el tratamiento de un sujeto que sufre de una enfermedad o un trastorno asociado con la actividad de TLR, donde los métodos incluyen la administración al sujeto, de una cantidad eficaz de un compuesto de la Fórmula (I) o de una sal aceptable para uso farmacéutico, un solvato, ya sea solos, ya sea como parte de una composición farmacéutica como se describe en la presente solicitud.

Se provee en la presente solicitud el uso de un compuesto de la Fórmula (I), o de una sal aceptable para uso farmacéutico o de un solvato de dicho

compuesto, en la preparación de un medicamento para el tratamiento de una enfermedad o un trastorno asociado con la actividad de TLR. En ciertas realizaciones, un compuesto de la Fórmula (I), o una sal aceptable para uso farmacéutico o un solvato de dicho compuesto, se usa en la preparación de un medicamento para el tratamiento de una enfermedad o un trastorno asociado con TLR7. En ciertas realizaciones, un compuesto de la Fórmula (I), o una sal aceptable para uso farmacéutico o un solvato de dicho compuesto, se usa en la preparación de un medicamento para el tratamiento de una enfermedad o un trastorno asociado con TLR8.

En una realización adicional, las composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula (I) se adaptan para la administración oral para el tratamiento de enfermedades y trastornos virales asociados con la actividad de TLR7 o TLR8.

En una realización adicional, las composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula (I) se adaptan para la administración oral para el tratamiento de enfermedades y trastornos infecciosos asociados con la actividad de TLR7 o TLR8.

En una realización adicional, las composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula (I) se adaptan para la administración oral para el tratamiento de enfermedades y trastornos bacterianos asociados con la actividad de TLR7 o TLR8.

En una realización adicional, las composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula (I) se adaptan para la administración oral para el tratamiento de enfermedades y trastornos fúngicos asociados con la actividad de TLR7 o TLR8.

En una realización adicional, las composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula (I) se adaptan para la

administración oral para el tratamiento de cáncer asociado con la actividad de TLR7 o TLR8.

En una realización adicional, las composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula (I) se adaptan para la administración intravenosa para el tratamiento de cáncer asociado con la actividad de TLR7 o TLR8.

En una realización adicional, las composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula (I) se adaptan para la administración oral para el tratamiento de enfermedades y trastornos de rechazo de aloinjertos asociados con la actividad de TLR7 o TLR8.

En una realización adicional, las composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula (I) se adaptan para la administración oral para el tratamiento de enfermedades y trastornos genitourinarios asociados con la actividad de TLR7 o TLR8.

En una realización adicional, las composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula (I) se adaptan para la administración como gotas oculares para el tratamiento de enfermedades y trastornos oftálmicos asociados con la actividad de TLR7 o TLR8.

En una realización adicional, las composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula (I) se adaptan para la administración tópica para el tratamiento de enfermedades y trastornos dermatológicos asociados con la actividad de TLR7 o TLR8.

En una realización adicional, las composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula (I) se adaptan para la administración tópica para el tratamiento de queratosis actínica. En una realización adicional, las composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula (I) se adaptan para la administración tópica

como una crema para el tratamiento de queratosis actínica.

En una realización adicional, las composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula (I) se adaptan para la administración tópica para el tratamiento de carcinoma de célula basal. En una realización adicional, las composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula (I) se adaptan para la administración tópica como una crema para el tratamiento de carcinoma de célula basal.

En una realización adicional, las composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula (I) se adaptan para la administración por inhalación, para el tratamiento de enfermedades o trastornos respiratorios asociados con la actividad de TLR7 o TLR8. En ciertas realizaciones, la enfermedad respiratoria es asma alérgica.

Tratamiento de combinación.

En ciertas realizaciones, un compuesto de las Fórmulas (I)–(XVI) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, o una composición farmacéutica que contiene por lo menos un compuesto de las Formulas (I)–(XVI) descripto en la presente solicitud, se administra solo (sin un agente terapéutico adicional) para el tratamiento de una o más de las enfermedades y los trastornos asociados con la actividad de TLR descriptos en la presente solicitud.

En otras realizaciones, un compuesto de las Fórmulas (I)–(XVI) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, o una composición farmacéutica que contiene por lo menos un compuesto de las Formulas (I)–(XVI) descripto en la presente solicitud, se administra en combinación con uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y los trastornos asociados con

la actividad de TLR descriptos en la presente solicitud.

En otras realizaciones, un compuesto de las Fórmulas (I)–(XVI) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, o una composición farmacéutica que contiene por lo menos un compuesto de las Formulas (I)–(XVI) descripto en la presente solicitud, se formula en combinación con uno o más agentes terapéuticos adicionales, y se administra para el tratamiento de una o más de las enfermedades y los trastornos asociados con la actividad de TLR descriptos en la presente solicitud.

Un compuesto de las Fórmulas (I)–(XVI) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, o una composición farmacéutica que contiene por lo menos un compuesto de las Formulas (I)–(XVI) descripto en la presente solicitud, se administra en forma sucesiva con uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y los trastornos asociados con la actividad de TLR descriptos en la presente solicitud.

En otras realizaciones, los tratamientos de combinación provistos en la presente solicitud incluyen la administración de un compuesto de las Fórmulas (I)–(XVI) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, o una composición farmacéutica que contiene un compuesto de las Formulas (I)–(XVI), antes de la administración de uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y los trastornos asociados con la actividad de TLR descriptos en la presente solicitud.

En otras realizaciones, los tratamientos de combinación provistos en la presente solicitud incluyen la administración de un compuesto de las Fórmulas (I)–(XVI) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, o una composición farmacéutica que

contiene un compuesto de las Formulas (I)–(XVI), luego de la administración de uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y los trastornos asociados con la actividad de TLR descriptos en la presente solicitud.

En ciertas realizaciones, los tratamientos de combinación provistos en la presente solicitud incluyen la administración de un compuesto de las Fórmulas (I)–(XVI) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, o una composición farmacéutica que contiene un compuesto de las Formulas (I)–(XVI), en forma concurrente con uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y los trastornos asociados con la actividad de TLR descriptos en la presente solicitud.

En ciertas realizaciones, los tratamientos de combinación provistos en la presente solicitud incluyen la administración de un compuesto de las Fórmulas (I)–(XVI) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, o una composición farmacéutica que contiene un compuesto de las Formulas (I)–(XVI), formulado con uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y los trastornos asociados con la actividad de TLR descriptos en la presente solicitud.

En ciertas realizaciones de los tratamientos de combinación descriptos en la presente solicitud, los compuestos de la Fórmula (I), o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, son moduladores de la actividad de TLR. En ciertas realizaciones de los tratamientos de combinación descriptos en la presente solicitud, los compuestos de la Fórmula (I), o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, son agonistas de TLR7. En ciertas realizaciones de los tratamientos de combinación descriptos en

la presente solicitud, los compuestos de la Fórmula (I), o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, son agonistas de TLR8.

En ciertas realizaciones de los tratamientos de combinación descriptos en la presente solicitud, los compuestos de la Fórmula (I), aquí descriptos, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, y los agentes terapéuticos adicionales actúan en forma aditiva. En ciertas realizaciones de los tratamientos de combinación descriptos en la presente solicitud, los compuestos de la Fórmula (I), aquí descriptos, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, y los agentes terapéuticos adicionales actúan en forma sinérgica.

En otras realizaciones, un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, o una composición farmacéutica que contiene un compuesto de la Fórmula (I), se administra a un paciente que no ha sido sometido previamente o que no es actualmente sometido a tratamiento con otro agente terapéutico.

Los agentes terapéuticos adicionales utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, antibióticos o agentes antibacterianos, agentes antieméticos, agentes antifúngicos, agentes antiinflamatorios, agentes antivirales, agentes inmunomoduladores, citoquinas, antidepresivos, hormonas, agentes alquilantes, antimetabolitos, antibióticos antitumorales, agentes antimitóticos, inhibidores de la topoisomerasa, agentes citostáticos, agentes antiinvasivos, agentes antiangiogénicos, inhibidores de la función de factores de crecimiento, inhibidores de la replicación viral, inhibidores de enzimas virales, agentes antineoplásicos, α–interferones, β–interferones, ribavirina, hormonas, citoquinas y otros moduladores de receptores de tipo toll.

Los antibióticos o agentes antibacterianos utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, valganciclovir clorhidrato, metronidazol, un beta–lactámico, macrólidos (tales como, solo a modo de ejemplo, azitromicina, tobramicina (TOBI™)), cefalosporinas (tales como, solo a modo de ejemplo, cefaclor, cefadroxilo, cefalexina, cefradina, cefamandol, cefatrizina, cefazedona, cefixima, cefozoprano, cefpimizol, cefuroxima, cefpiramida, cefprozilo, cefpiroma, KEFLEX™, VELOSEF™, CEFTIN™, CEFZIL™, CECLOR™, SUPRAX™ y DURICEF™), una claritromicina (tal como, solo a modo de ejemplo, claritromicina y BIAXIN™), una eritromicina (tal como, solo a modo de ejemplo, eritromicina y EMYCIN™), ciprofloxacina, CIPRO™, una norfloxacina (tal como, solo a modo de ejemplo, NOROXIN™), antibióticos de aminoglucósidos (tales como, solo a modo de ejemplo, apramicina, arbekacina, bambermicinas, butirosina, dibekacina, neomicina, neomicina undecilenato, netilmicina, paromomicina, ribostamicina, sisomicina y espectinomicina), antibióticos de anfenicol (tales como, solo a modo de ejemplo, azidanfenicol, cloranfenicol, florfenicol y tianfenicol), antibióticos de ansamicina (tales como, solo a modo de ejemplo, rifamida y rifampina), carbacefémicos (tales como, solo a modo de ejemplo, loracarbef), carbapenémicos (tales como, solo a modo de ejemplo, biapenem e imipenem), cefamicinas (tales como, solo a modo de ejemplo, cefbuperazona, cefmetazol y cefminox), monobactámicos (tales como, solo a modo de ejemplo, aztreonam, carumonam y tigemonam), oxacefémicos (tales como, solo a modo de ejemplo, flomoxef y moxalactama), penicilinas (tales como, solo a modo de ejemplo, amdinocilina, amdinocilina pivoxilo, amoxicilina, bacampicilina, ácido bencilpenicilínico, bencilpenicilina sódica, epicilina, fenbenicilina, floxacilina, penamccilina, penetamato yodhidrato, penicilina o–benetamina, penicilina 0,

penicilina V, penicilina V benzatina, penicillna V hidrabamina, penimepiciclina, fencihicilina potásica, V–CILLIN K™ y PEN VEE K™), lincosamidas (tales como, solo a modo de ejemplo, clindamicina y lincomicina), anfomicina, bacitracina, capreomicina, colistina, enduracidina, enviomicina, tetraciclinas (tales como, solo a modo de ejemplo, apiciclina, clortetraciclina, clomociclina y demeclociclina), 2,4–diaminopirimidinas (tales como, solo a modo de ejemplo, brodimoprim), nitrofuranos (tales como, solo a modo de ejemplo, furaltadona y cloruro de furazolio), quinolonas y sus análogos (tales como, solo a modo de ejemplo, fluorquinolona, ofloxacina, cinoxacina, clinafloxacina, flumequina, grepagloxacina y FLOXIN™), sulfonamidas (tales como, solo a modo de ejemplo, acetil sulfametoxipirazina, bencilsulfamida, noprilsulfamida, ftalilsulfacetamida, sulfacrisoidina y sulfacitina), sulfonas (tales como, solo a modo de ejemplo, diatimosulfona, glucosulfona sódica y solasulfona), cicloserina, mupirocina, tuberina y sus combinaciones.

Los agentes antieméticos utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, metoclopromida, domperidona, proclorperazina, prometazina, clorpromazina, trimetobenzamida, ondansetrona, granisetrona, hidroxizina, acetileucina monoetanolamina, alizaprida, azasetrona, benzquinamida, bietanautina, bromoprida, buclizina, cleboprida, ciclizina, dimenhidrinato, difenidol, dolasetrona, meclizina, metalatal, metopimazina, nabilona, oxiperndilo, pipamazina, escopolamina, sulpirida, tetrahidrocanabinoles, tietilperazina, tioproperazina, tropisetrona y sus combinaciones.

Los agentes antifúngicos utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin

limitación, anfotericina B, itraconazol, cetoconazol, fluconazol, fosfluconazol, intratocal, flucitosina, miconazol, butoconazol, itraconazol, clotrimazol, nistatina, terconazol, tioconazol, voriconazol, ciclopirox, econazol, haloprogrina, naftifina, terbinafina, undecilenato y griseofulvina.

Los agentes antiinflamatorios utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, fármacos antiinflamatorios no corticoesteroides, tales como ácido salicílico, ácido acetilsalicílico, metil salicilato, diflunisal, salsalato, olsalazina, sulfasalazina, acetaminofeno, indometacina, sulindac, etodolac, ácido mefenámico, meclofenamato sódico, tolmetina, cetorolac, diclofenac, ibuprofeno, naproxeno, naproxeno sódico, fenoprofeno, cetoprofeno, flurbinprofeno, oxaprozina, piroxicam, meloxicam, ampiroxicam, droxicam, pivoxicam, tenoxicam, nabumetoma, fenilbutazona, oxifenbutazona, antipirina, aminopirina, apazona y nimesulida; antagonistas de leucotrieno, entre ellos, sin limitación, zileutona, aurotioglucosa, tiomalato sódico de oro y auranofina; corticoesteroides, entre ellos, sin limitación, alclometasona diproprionato, amcinonida, beclometasona dipropionato, betametasona, betametasona benzoato, betametasona diproprionato, betametasona sódica fosfato, betametasona valerato, clobetasol proprionato, clocortolona pivalato, hidrocortisona, derivados de hidrocortisona, desonida, desoximatasona, dexametasona, flunisolida, flucoxinolida, flurandrenolida, halcinocida, medrisona, metilprednisolona, metprednisolona acetato, metilprednisolona sódica succinato, mometasona furoato, parametasona acetato, prednisolona, prednisolona acetato, prednisolona sódica fosfato, prednisolona tebuatato, prednisona, triamcinolona, triamcinolona acetonida, triamcinolona diacetata y triamcinolona hexacetonida y otros agentes antiinflamatorios que incluyen, sin limitación, metotrexato, colchicina, alopurinol,

probenecid, talidomida o uno de sus derivados, ácido 5–aminosalicílico, retinoides, ditranol o calcipotriol, sulfinpirazona y benzbromarona.

Los agentes antivirales utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, inhibidores de la proteasa, inhibidores de la transcriptasa inversa de nucleósido/nucleótido (NRTI, por sus siglas en inglés), inhibidores de la transcriptasa inversa no nucleósidos (NNRTI, por sus siglas en inglés), antagonistas de CCR1, antagonistas de CCR5 y análogos de nucleósidos. Los agentes antivirales incluyen, sin limitación, fomivirseno, didanosina, lamivudina, estavudina, zalcitabina, zidovudina, aciclovir, famciclovir, valaciclovir, ganciclovir, gangciclovir, cidofovir, zanamivir, oseltamavir, vidarabina, idoxuridina, trifluridina, levovirina, viramidina y ribavirina, al igual que foscarnet, amantadina, rimantadina, saquinavir, indinavir, nelfinavir, amprenavir, lopinavir, ritonavir, α–interferones; β–interferones; adefovir, clevadina, entecavir, pleconarilo, HCV–086, EMZ702, emtricitabina, celgosivir, valopicitabina, inhibidores de proteasa de HCV, tales como BILN 2061, SCH–503034, ITMN–191 o VX–950; inhibidores de NS5B polimerasa tales como NM107 (y su profármaco NM283), R1626, R7078, BILN1941, GSK625433, GILD9128 o HCV–796, efavirenz, HBY–097, nevirapina, TMC–120 (dapivirina), TMC–125, BX–471, etravirina, delavirdina, DPC–083, DPC–961, capravirina, rilpivirina, 5–{[3,5–dietil–1–(2–hidroxietil)–1H–pirazol–4–il]oxi}isoftalonitrilo, GW–678248, GW–695634, MIV–150, calanolida, TAK–779, SC–351125, ancriviroc, vicriviroc, maraviroc, PRO–140, aplaviroc 40, Ono–4128, AK–602), AMD–887 CMPD–167, metil 1–endo–{8–[(3S)–3–(acetilamino)–3–(3–fluorfenil)propil]–8–azabiciclo[3.–2.1]oct–3–il}–2–metil–4,5,6,7–tetrahidro–1H–imidazo[4,5–c]piridina–5–carboxilato, metil 3–endo–{8–[(3S)–3–(acetamido)–3–(3–fluorfenil)propil]–8–azabiciclo[3.2.–1]oct–3–il}–2–metil–4,5,6,7–tetrahidro–3H–

imidazo[4,5–c]piridina–5–carboxilato, etil 1–endo–{8–[(3S)–3–(acetilamino)–3–(3–fluorfenil)propil]–8–azabiciclo[3.–2.1]oct–3–il}–2–metil–4,5,6,7–tetrahidro–1H–imidazo[4,5–c]piridina–5–carboxilato y N–{(1S)–3–[3–endo–(5–Isobutiril–2–metil–4,5,6,7–tetrahidro–1H–imidazo[4,–5–c]piridin–1–il)–8–azabiciclo[3.2.1]oct–8–il]–1–(3–fluorfenil)propil}acetamida), BMS–806, BMS–488043, ácido 5–{(1S)–2–[(2R)–4–benzoil–2–metil–piperazin–1–il]–1–metil–2–oxo–etoxi}–4–metoxi–piridina–2–carboxílico metilamida y 4–{(1S)–2–[(2R)–4–benzoil–2–metil–piperazin–1–il]–1–metil–2–oxo–etoxi}–3–metoxi–N–metil–benzamida, enfuvirtida (T–20), sifuvirtida SP–01A, T1249, PRO 542, AMD–3100, CD4 soluble, inhibidores de HMG CoA reductasa, atorvastatina, ácido 3–O–(3'3'–dimetilsucinil) betúlico (conocido de otro modo como PA–457) y αHGA.

Los agentes inmunomoduladores utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, azatioprina, tacrolimus, ciclosporina metotrexato, leflunomida, corticoesteroides, ciclofosfamida, ciclosporina A, ciclosporina G, micofenolato mofetilo, ascomicina, rapamicina (sirolimus), FK–506, mizoribina, deoxiespergualina, brequinar, ácido micofenólico, malononitriloamidas (tales como, solo a modo de ejemplo, leflunamida), moduladores de receptores de células T y moduladores de receptores de citoquinas, mímétidos peptídicos y anticuerpos (tales como, solo a modo de ejemplo, anticuerpos humanos, humanizados, quiméricos, monoclonales, policlonales, fragmentos Fvs, ScFvs, Fab o F(ab)2 o fragmentos de unión de epítopo), moléculas de ácido nucleico (tales como, solo a modo de ejemplo, moléculas de ácido nucleico antisentido y hélices triples), moléculas pequeñas, compuestos orgánicos y compuestos inorgánicos. Ejemplos de moduladores de receptores de células T abarcan, sin limitación, anticuerpos antirreceptores de células T (tales como, solo a modo de

ejemplo, anticuerpos anti–CD4 (solo a modo de ejemplo, cM–T412 (Boehringer), IDEC–CE9.1™ (IDEC y SKB), mAB 4162W94, Orthoclone y OKTcdr4a (Janssen–Cilag)); anticuerpos anti–CD3 (tales como, solo a modo de ejemplo, Nuvion (Product Design Labs), OKT3 (Johnson & Johnson), o Rituxan (IDEC)); anticuerpos anti–CD5 (tales como, solo a modo de ejemplo, un inmunoconjugado ligado a ricina anti–CD5); anticuerpos anti–CD7 (tales como, solo a modo de ejemplo, CHH–380 (Novartis)); anticuerpos anti–CD8; anticuerpos monoclonales ligandos anti–CD40 (tales como, solo a modo de ejemplo, IDEC–131 (IDEC)); anticuerpos anti–CD52 (tales como, solo a modo de ejemplo, CAMPATH 1H (Ilex)); anticuerpos anti–CD2; anticuerpos anti–CD11a (tales como, solo a modo de ejemplo, Xanelim (Genentech)); anticuerpos anti–B7 (tales como, solo a modo de ejemplo, IDEC–114 (IDEC)); CTLA4–inmunoglobulina, y otros moduladores de tipo receptor toll (TLR). Ejemplos de moduladores de receptores de citoquinas incluyen, sin limitación, receptores de citoquinas solubles (tales como, solo a modo de ejemplo, el dominio extracelular de un receptor de TNF–α o uno de sus fragmentos; el dominio extracelular de un receptor de IL–1β o uno de sus fragmentos; y el dominio extracelular de un receptor de IL–6 o uno de sus fragmentos); citoquinas o sus fragmentos (tales como, solo a modo de ejemplo, interleuquina (IL)–2, IL–3, IL–4, IL–5, IL–6, IL–7, IL–8, IL–9, IL–10, IL–11, IL–12, IL–15, TNF–.alfa., interferón (IFN)–α, IFN–β, IFN–γ y GM–CSF); anticuerpos antirreceptores de citoquinas (tales como, solo a modo de ejemplo, anticuerpos antirreceptores de IFN; anticuerpos antirreceptores de IL–2 (tales como, solo a modo de ejemplo, Zenapax (Protein Design Labs)); anticuerpos antirreceptores de IL–4; anticuerpos antirreceptores de IL–6; anticuerpos antirreceptores de IL–10 y anticuerpos antirreceptores de IL–12); anticuerpos anticitoquinas (tales como, solo a modo de ejemplo, anticuerpos anti–IFN, anticuerpos anti–TNF–α, anticuerpos anti–IL–1β, anticuerpos anti–IL–6, anticuerpos anti–IL–8 (tales como, solo a modo

de ejemplo, ABX–IL–8 (Abgenix)) y anticuerpos anti–IL–12).

Las citoquinas o los moduladores de la función de citoquina utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, interleuquina–2 (IL–2), interleuquina–3 (IL–3), interleuquina–4 (IL–4), interleuquina–5 (IL–5), interleuquina–6 (IL–6), interleuquina–7 (IL–7), interleuquina–9 (IL–9), interleuquina–10 (IL–10), interleuquina–12 (IL–12), interleuquina 15 (IL–15), interleuquina 18 (IL–18), factor de crecimiento derivado de plaqueta (PDGF), eritropoietina (Epo), factor de crecimiento epidérmico (EGF), factor de crecimiento de fibroblastos (FGF), factor estimulante de granulocitos macrófagos (GM–CSF), factor estimulante de colonias de granulocitos (G–CSF), factor estimulante de colonia de macrófagos (M–CSF), prolactina, alfa–, beta– y gamma–interferones, interferón β–1a, interferón β–1b, interferón α–1, interferón α–2a (roferón), interferón α–2b, interferones pegilados (solo a modo de ejemplo, peginterferón α–2a y peginterferón α–2b), intrón, Peg–Intron, Pegasys, interferón de consenso (infergen), albúmina–interferón α y albuferón.

Los antidepresivos utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, binedalina, caroxazona, citalopram, dimetazan, fencamina, indalpina, indeloxazina clorhidrato, nefopam, nomifensina, oxitriptano, oxipertina, paroxetina, sertralina, tiazesim, trazodona, benmoxina, echinopsidina yoduro, etriptamina, iproclozida, iproniazid, isocarboxazid, mebanazina, metfendrazina, nialamida, pargilina, octamoxina, fenelzina, feniprazina, fenoxipropazina, pivhidrazina, safrazina, selegilina, l–deprenilo, cotinina, roliciprina, rolipram, maprotilina, metralindol, mianserina, mirtazepina, adinazolam, amitriptilina, amitriptilinóxido,

amoxapina, butriptilina, clomipramina, demexiptilina, desipramina, dibencepina, dimetacrina, dotiepina, doxepina, fluacizina, imipramina, imipramina N–óxido, iprindol, lofepramina, melitraceno, metapramina, nortriptilina, noxiptilina, opipramol, pizotilina, propizepina, protriptilina, quinupramina, tianeptina, trimipramina, adrafinilo, benactizina, bupropión, butacetina, dioxadrol, duloxetina, etoperidona, febarbamato, femoxetina, fenpentadiol, fluoxetina, fluvoxamina, hematoporfirina, hipericina, levofacetoperano, medifoxamina, milnaciprano, minaprina, moclobemida, nefazodona, oxaflozano, piberalina, prolintano, pirisuccideanol, ritanserina, roxindol, rubidio cloruro, sulpirida, tandospirona, tozalinona, tofenacina, toloxatona, tranilcipromina, L–triptófano, venlafaxina, viloxazina y zimeldina.

En ciertas realizaciones, los antidepresivos utilizados en combinación con por lo menos un compuesto de la Fórmula (I) como se describe en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, son inhibidores de MAO (monoamina oxidasa) que incluyen, sin limitación, benmoxina, echinopsidina yoduro, etriptamina, iproclozida, iproniazid, isocarboxazid, mebanazina, metfendrazina, moclobamida, nialamida, pargilina, fenelzina, feniprazina, fenoxipropazina, pivhidrazina, safrazina, selegilina, l–deprenilo, toloxatona y tranilcipromina.

Las hormonas utilizadas en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, hormona liberadora de la hormona luteinizante (LHRH, por sus siglas en inglés), hormona de crecimiento (GH, por sus siglas en inglés), hormona liberadora de la hormona de crecimiento, ACTH (siglas en inglés de la hormona adrenocorticotropina), somatostatina, somatotropina, somatomedina, hormona paratiroidea, factores de liberación hipotalámicos, insulina, glucagón, encefalinas,

vasopresina, calcitonina, heparina, heparinas de bajo peso molecular, heparinoides, timoestimulina, opioides naturales y sintéticos, hormonas estimulantes tiroideas insulínicas y endorfinas.

Los agentes alquilantes utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, mostazas de nitrógeno, etileniminas, metilmelaminas, alquil sulfonatos, nitrosoureas, carmustina, lomustina, triazenos, melfalano, mecloretamina, cis–platino, oxaliplatino, carboplatino, ciclofosfamida, ifosfamida, melfalano, cloranbucilo, hexametilmelaína, tiotepa, busulfano, carmustina, estreptozocina, dacarbazina y temozolomida.

Los antimetabolitos utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, citarabilo, gemcitabina y antifolatos tales como, solo a modo de ejemplo, fluorpirimidinas (solo a modo de ejemplo, 5–fluoruracilo y tegafur), raltitrexed, metotrexato, citosina arabinosida e hidroxiurea.

Los antibióticos antitumorales utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, antraciclinas, bleomicina, doxorrubicina, daunomicina, epirrubicina, idarrubicina, mitomicina–C, dactinomicina y mitramicina.

Los agentes antimitóticos utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, alcaloides de la especie *Vinca rosea* (solo a modo de ejemplo, vincristina, vinblastina, vindesina y vinorrelbina), taxoides (solo a modo de

ejemplo, taxol, paclitaxel y taxotero) e inhibidores de poloquinasa.

Los inhibidores de la topoisomerasa utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, epipodofilotoxinas, tales como, solo a modo de ejemplo, etoposida y teniposida; amsacrina, topotecano, irinotecano y camptotecina.

Los agentes citostáticos utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, antiestrógenos (tales como, solo a modo de ejemplo, tamoxifeno, fulvestrant, toremifeno, raloxifeno, droloxifeno y yodoxifeno), antiandrógenos (tales como, solo a modo de ejemplo, bicalutamida, flutamida, nilutamida y acetato de ciproterona), antagonistas de LHRH o agonistas de LHRH (tales como, solo a modo de ejemplo, goserrelina, leuprorrelina, leuprolida y buserrelina), progestágenos (tales como, solo a modo de ejemplo, megestrol acetato), inhibidores de la aromatasa (tales como, solo a modo de ejemplo, anastrozol, letrozol, vorazol y exemestano) e inhibidores de 5α–reductasa (tales como, solo a modo de ejemplo, finasterida).

Los agentes antiinvasivos utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, inhibidores de la familia de quinasas c–Src (tales como, solo a modo de ejemplo, 4–(6–cloro–2,3– metilenodioxianilino)–7–[2–(4–metilpiperazin–l–il)etoxi]–5–tetrahidropiran–4–iloxiquinazolina (AZD0530) y N–(2– cloro–6–metilfenil)–2–{6–[4–(2–hidroxietil)piperazin–l–il]–2–metilpirimidin–4–ilamino}tiazol–5–carboxamida (dasatinib, BMS–354825)), e inhibidores de metaloproteinasa (tales como, solo a modo de ejemplo, marimastat, inhibidores de la función del receptor de activador

de plasminógeno de uroquinasa, anticuerpos para Heparanase).

Los agentes antiangiogénicos utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, aquellos que inhiben los efectos del factor de crecimiento endotelial vascular, tales como, solo a modo de ejemplo, el anticuerpo antifactor de crecimiento celular endotelial bevacizumab (AVASTIN™) e inhibidores de tirosina quinasa de receptor VEGF tales como 4–(4–bromo– 2–fluoranilino)–6–metoxi–7–(l–metilpiperidin–4–ilmetoxi)quinazolina (ZD6474), 4–(4–fluor–2–metilindol–5–iloxi)–6–metoxi–7–(3–pirrolidin–1–ilpropoxi)quinazolina (AZD2171), vatalanib (PTK787) y SUI 1248 (sunitinib), linomida, e inhibidores de la función de integrina αvβ3 y angioestatina.

Los inhibidores de la función del factor de crecimiento utilizados en combinación con por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o con una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, incluyen, sin limitación, anticuerpos de factor de crecimiento y anticuerpos de receptor de factor de crecimiento (tales como, solo a modo de ejemplo, al anticuerpo anti–erbB2 trastuzumab (HERCEPTIN™), el anticuerpo anti–EGFR panitumumab, el anticuerpo anti–erbBl cetuximab (Erbitux, C225), inhibidores de tirosina quinasa, tales como, solo a modo de ejemplo, inhibidores de la familia de factores de crecimiento epidérmico (por ejemplo, inhibidores de tirosina quinasa de la familia EGFR, tales como, solo a modo de ejemplo, N–(3–cloro–4–fluorfenil)–7–metoxi–6–(3–orfolinopropoxi)quinazolin–4–amina (gefitinib, ZDl 839), N–(3–etinilfenil)–6,7–bis(2–metoxietoxi)quinazolin–4–amina (erlotinib, OSI–774) y 6–acrilamido–N–(3–cloro–4–fluorfenil)–7–(3–morfolinopropoxi)–quinazolin–4–amina (Cl 1033), inhibidores de tirosina quinasa erbB2 tales como, solo a modo de ejemplo, lapatinib; inhibidores de la familia de factores de

crecimiento de hepatocitos; inhibidores de la familia de factores de crecimiento derivados de plaquetas, tales como imatinib, GLEEVEC™; inhibidores de serina/treonina quinasas (tales como, solo a modo de ejemplo, inhibidores de la señalización de Ras/Raf tales como inhibidores de farnesil transferasa, por ejemplo, sorafenib (BAY 43–9006)); inhibidores de la señalización celular a través de MEK y/o AKT quinasas; inhibidores de la familia de factores de crecimiento de hepatocitos; inhibidores de c–kit; inhibidores de abl quinasa; inhibidores de quinasas de receptor IGF (factor de crecimiento de tipo insulínico); inhibidores de aurora quinasa (por ejemplo, AZDI 152, F739358, VX–680, MLv8054, R763, MP235, MP529, VX–528 y AX39459) e inhibidores de quinasas dependientes de ciclina tales como inhibidores de CDK2 y/o CDK4.

En otras realizaciones, por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, se usa en combinación con agentes para el daño vascular, tales como, solo a modo de ejemplo, Combretastatin A4.

En otras realizaciones, por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, se usa en combinación con tratamientos antisentido, tales como, solo a modo de ejemplo, ISIS 2503, un antisentido anti–ras.

En otras realizaciones, por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, se usa en combinación con enfoques de terapia génica, que incluyen, por ejemplo, enfoques para el reemplazo de genes aberrantes tales como enfoques para el gen aberrante p53 o los genes aberrantes BRCAI o BRCA2, GDEPT (terapia de profármaco enzimática dirigida a genes), tales como aquellos que utilizan citosina deaminasa, timidina quinasa o una

enzima nitrorreductasa bacteriana; y enfoques para incrementar la tolerancia del paciente a la quimioterapia o radioterapia, tales como la terapia génica de resistencia a múltiples fármacos.

En otras realizaciones, por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, se usa en combinación con enfoques de inmunoterapia, que incluyen, por ejemplo, enfoques *ex–vivo* e *in–vivo* para incrementar la inmunogenicidad de células tumorales del paciente, tales como la transfección con citoquinas tales como interleuquina 2, interleuquina 4 o factor estimulante de colonias de granulocitos–macrófagos; enfoques para disminuir la anergia de células T; enfoques que utilizan células inmunitarias transfectadas, tales como células dendríticas transfectadas con citoquinas; enfoques que utilizan estirpes celulares tumorales transfectadas con citoquinas; y enfoques que utilizan anticuerpos antiidiopáticos.

En otras realizaciones, por lo menos un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, se usa en combinación con otros métodos de tratamiento, que incluyen, sin limitación, cirugía y radioterapia (radiación γ, radioterapia de rayo neutrónico, radioterapia de rayo electrónico, terapia protónica, braquiterapia e isótopos radiactivos sistémicos).

En ciertas realizaciones, los compuestos de la Fórmula (I) descriptos en la presente solicitud, o sus sales aceptables para uso farmacéutico y sus solvatos, se administran o se formulan en combinación con un mejorador de la absorción, que incluye, sin limitación, glicocolato de sodio, caprato de sodio, N–lauril–β–D–maltopiranosida, EDTA y micelas mixtas. En ciertas realizaciones, dichos mejoradores de la absorción se dirigen al sistema linfático.

En ciertas realizaciones, los agentes terapéuticos adicionales utilizados en

los tratamientos de combinación descriptos en la presente solicitud incluyen, sin limitación, agentes tales como inhibidores de factor alfa de necrosis tumoral (TNF–α) (tales como anticuerpos monoclonales anti–TNF (solo a modo de ejemplo, Remicade, CDP–870 y adalimumab) y moléculas de inmunoglobulina de receptor de TNF (solo a modo de ejemplo, Enbrel)); inhibidores no selectivos de ciclooxigenasa COX–I/COX–2 (solo a modo de ejemplo, piroxicam, diclofenac, ácidos propiónicos tales como naproxeno, flubiprofeno, fenoprofeno, cetoprofeno e ibuprofeno; fenamatos tales como ácido mefenámico, indometacina, sulindac, azapropazona, pirazolonas tales como fenilbutazona, salicilatos tales como aspirina); inhibidores de COX–2 (solo a modo de ejemplo, meloxicam, celecoxib, rofecoxib, valdecoxib, lumarocoxib, parecoxib y etoricoxib); glucocorticoesteroids; metotrexato, lefunomida; hidroxicloroquina, d–penicilamina, auranofina u otras preparaciones de oro orales o parenterales.

En otras realizaciones, las combinaciones que se describen en esta solicitud comprenden combinación de un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, con un inhibidor de la biosíntesis de leucotrieno, inhibidor de 5–lipoxigenasa (5–LO) o antagonista de proteína activadora de 5–lipoxigenasa (FLAP) tal como zileutona; ABT–761; fenleutona; tepoxalina; Abbott–79175; Abbott–85761; una N–(5–sustituido)–tiofeno–2–alquilsulfonamida; 2,6–di–ter–butilfenolhidrazonas; metoxitetrahidropiranos tales como Zeneca ZD–2138; el compuesto SB–210661; un compuesto de 2–cianonaftaleno piridinil–sustituido, tal como L–739,010; un compuesto de 2–cianoquinolina tal como L–746,530; o un compuesto de indol o quinolina tal como MK–591, MK–886 y BAYx1005.

En otras realizaciones, las combinaciones que se describen en esta solicitud comprenden combinación de un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o

uno de sus solvatos, con un antagonista para el receptor de leucotrienos (LT B4, LTC4, LTD4 y LTE4) seleccionado del grupo que consiste en los fenotiazin–3–les tales como L–651,392; compuestos de amidino tales como CGS–25019c; benzoxalaminas tales como ontazolast; bencenocarboximidamidas tales como BIIL 284/260; y compuestos tales como zafirlukast, ablukast, montelukast, SINGULAIR™, pranlukast, verlukast (MK–679), RG–12525, Ro–245913, iralukast (CGP 45715A) y BAYx7195.

En otras realizaciones, las combinaciones que se describen en esta solicitud comprenden combinación de un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, con un inhibidor de fosfodiesterasa (PDE, por sus siglas en inglés) tal como una metilxantanina, que incluye teofillina y aminofillina; un inhibidor selectivo de isoenzima PDE que incluye un inhibidor de PDE4, por ejemplo, sin limitación, cilomilast o roflumilast; un inibidor de la isoforma PDE4D, o un inhibidor de PDE5.

En otras realizaciones, las combinaciones que se describen en esta solicitud comprenden combinación de un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, con un antagonista del receptor de tipo 1 de histamina, tal como cetirizina, loratadina, desloratadina, fexofenadina, acrivastina, terfenadina, astemizol, azelastina, levocabastina, clorfeniramina, prometazina, ciclizina, o mizolastina.

En otras realizaciones, las combinaciones que se describen en esta solicitud comprenden combinación de un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, con un antagonista del receptor de tipo 2 de histamina gastroprotector. En otras realizaciones, las combinaciones que se describen en

esta solicitud comprenden combinación de un compuesto de la Fórmula (I), o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, descriptos en la presente solicitud, con un antagonista del receptor de tipo 4 de histamina.

En otras realizaciones, las combinaciones que se describen en esta solicitud comprenden combinación de un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, con un agente simpatomimético vasoconstrictor agonista del receptor adrenérgico alfa1/alfa2, tal como propilhexedrina, fenilefrina, fenilpropanolamina, efedrina, pseudoefedrina, nafazolina clorhidrato, oximetazolina clorhidrato, tetrahidrozolina clorhidrato, xilometazolina clorhidrato, tramazolina clorhidrato o etilnorepinafrina clorhidrato.

En otras realizaciones, las combinaciones que se describen en esta solicitud comprenden combinación de un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, con un agente anticolinérgico que incluye antagonistas del receptor muscarínico (M1, M2, y M3) tales como atropina, hioscina, glicopirrrolato, ipratropio bromuro, tiotropio bromuro, oxitropio bromuro, pirenzepina o telenzepina.

En otras realizaciones, las combinaciones que se describen en esta solicitud comprenden combinación de un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, con un agonista del receptor adrenérgico beta (que incluye los subtipos de receptores beta 1–4), tales como isoprenalina, salbutamol, albuterol, formoterol, salmeterol, terbutalina, orciprenalina, bitolterol mesilato, y pirbuterol.

En otras realizaciones, las combinaciones que se describen en esta solicitud comprenden combinación de un compuesto de la Fórmula (I) descripto

en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, con una cromona, tal como cromoglicato de sodio o nedocromil sódico.

En otras realizaciones, las combinaciones que se describen en esta solicitud comprenden combinación de un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, con un mimético de tipo 1 de factor de crecimiento de tipo insulínico (IGF–I).

En otras realizaciones, las combinaciones que se describen en esta solicitud comprenden combinación de un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, con un glucocorticoide, tal como flunisolida, triamcinolona acetonida, beclometasona dipropionato, budesonida, fluticasona propionato, ciclesonida o mometasona furoato.

En otras realizaciones, las combinaciones que se describen en esta solicitud comprenden combinación de un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, con un inhibidor de metaloproteasas de matriz (MMP, por sus siglas en inglés), es decir, las estromelisinas, las colagenasas y las gelatinasas, al igual que agrecanasa; en especial, colagenasa–1 (MMP–I), colagenasa–2 (MMP–8), colagenasa–3 (MMP–13), estromelisina–1 (MMP–3), estromelisina–2 (MMP–IO) y estromelisina–3 (MMP–II), y MMP–9 y MMP–12.

En otras realizaciones, las combinaciones que se describen en esta solicitud comprenden combinación de un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, con moduladores de la función del receptor de quimioquina, tales como antagonistas de CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5,

CCR6, CCR7, CCR8, CCR9, CCR1O y CCR11 (para la familia C–C); CXCR1, CXCR2, CXCR3, CXCR4 y CXCR5 (para la familia C–X–C) y CX3CR1, para la familia C–X3–C.

En otras realizaciones, las combinaciones que se describen en esta solicitud comprenden combinación de un compuesto de la Fórmula (I) descripto en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, con una inmunoglobulina (Ig), gamma globulina, preparación de Ig o un antagonista o anticuerpo que modula la función de Ig, tal como anti–IgE (omalizumab).

Compuestos de la Fórmula (I) como potenciadores inmunitarios.

En ciertas realizaciones, las composiciones farmacéuticas que contienen por lo menos un compuesto de la Fórmula (I) como se describe en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, son composiciones inmunógenas. En ciertas realizaciones, dichas composiciones inmunógenas son útiles como vacunas. En ciertas realizaciones, dichas vacunas son profilácticas (es decir, previenen la infección), mientras que en otras realizaciones, dichas vacunas son terapéuticas (es decir, tratan la infección).

En otras realizaciones, los compuestos de la Fórmula (I) descriptos en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, son potenciadores inmunitarios, e imparten un efecto inmunoestimulante con la administración, cuando se comparan con formulaciones inmunógenas que no contienen compuestos de la Fórmula (I). En ciertas realizaciones, los compuestos de la Fórmula (I) imparten un efecto inmunoestimulante con la administración cuando se incluyen en una composición inmunógena que tiene uno o más agentes inmunorreguladores, mientras que en otras realizaciones, los compuestos de la Fórmula (I) imparten un efecto

inmunoestimulante con la administración, cuando se incluyen en una composición inmunógena sin la presencia de otros agentes inmunorreguladores.

El efecto inmunoestimulante al que se hace referencia en esta solicitud a menudo consiste en una mejoría del efecto de la composición inmunógena. En ciertas realizaciones, la mejoría de la eficacia de la composición inmunógena es al menos del 10%, en relación con el efecto de la composición inmunógena en ausencia del potenciador inmunógeno. En ciertas realizaciones, la mejoría de la eficacia de la composición inmunógena es al menos del 20%, en relación al efecto de la composición inmunógena en ausencia del potenciador inmunitario. En ciertas realizaciones, la mejoría de la eficacia de la composición inmunógena es al menos del 30%, en relación al efecto de la composición inmunógena en ausencia del potenciador inmunitario. En ciertas realizaciones, la mejoría de la eficacia de la composición inmunógena es al menos del 40%, en relación al efecto de la composición inmunógena en ausencia del potenciador inmunitario. En ciertas realizaciones, la mejoría de la eficacia de la composición inmunógena es al menos del 50%, en relación al efecto de la composición inmunógena en ausencia del potenciador inmunitario. En ciertas realizaciones, la mejoría de la eficacia de la composición inmunógena es al menos del 60%, en relación al efecto de la composición inmunógena en ausencia del potenciador inmunitario. En ciertas realizaciones, la mejoría de la eficacia de la composición inmunógena es al menos del 70%, en relación al efecto de la composición inmunógena en ausencia del potenciador inmunitario. En ciertas realizaciones, la mejoría de la eficacia de la composición inmunógena es al menos del 80%, en relación al efecto de la composición inmunógena en ausencia del potenciador inmunitario. En ciertas realizaciones, la mejoría de la eficacia de la composición inmunógena es al menos del 90%, en relación al efecto de la composición inmunógena en ausencia del potenciador inmunitario. En ciertas realizaciones, la mejoría de la eficacia de

la composición inmunógena es al menos del 100%, en relación al efecto de la composición inmunógena en ausencia del potenciador inmunitario.

En ciertas realizaciones, la mejoría del efecto de la composición inmunógena se mide por medio del incremento de la eficacia de la composición inmunógena para lograr sus efectos protectores. En ciertas realizaciones, esta mayor eficacia se mide como una menor probabilidad de que un sujeto que recibe la composición inmunógena experimente una afección para la cual la composición inmunógena se considera protectora, o como una disminución en la duración o gravedad de los efectos de dicha afección. En otras realizaciones, esta mayor eficacia se mide como un incremento en una valoración de un anticuerpo producido por la composición inmunógena en un sujeto tratado.

Junto con uno o más compuestos de la Fórmula (I) descriptos en la presente solicitud, o una de sus sales aceptables para uso farmacéutico o uno de sus solvatos, dichas composiciones inmunógenas incluyen una cantidad eficaz de uno o más antígenos, y un portador farmacéuticamente aceptable. Dichos portadores incluyen, sin limitación, proteínas, polisacáridos, ácidos polilácticos, ácidos poliglicólicos, aminoácidos poliméricos, copolímeros de aminoácidos, sacarosa, trehalosa, lactosa, agregados lípidos (tales como gotas de aceite o liposomas) y partículas virales inactivas. Las composiciones inmunógenas, en general, también contienen diluyentes, tales como agua, solución salina y glicerol, y opcionalmente, contienen otros excipientes, tales como agentes humectantes o emulsionantes y sustancias reguladoras del pH.

En ciertas realizaciones, las composiciones inmunógenas incluyen, en forma opcional, uno o más agentes inmunorreguladores. En ciertas realizaciones, uno o más de los agentes inmunorreguladores comprenden uno o más coadyuvantes. Dichos coadyuvantes incluyen, sin limitación, un coadyuvante TH1 o coadyuvante TH2, descriptos en mayor detalle a continuación. En ciertas

realizaciones, los coadyuvantes utilizados en las composiciones inmunógenas que se proveen en esta solicitud incluyen, sin limitación:

A. Composiciones que contienen minerales;

B. Emulsiones de aceite;

C. Formulaciones de saponinas;

D. Virosomas y partículas de tipo viral;

E. Derivados bacterianos o microbianos;

F. Inmunomoduladores humanos;

G. Bioadhesivos y Mucoadhesivos;

H. Micropartículas;

I. Liposomas;

J. Formulaciones de polioxietileno éter y polioxietileno éster;

K. Polifosfazeno (PCPP);

L. Péptidos de muramilo; y

M. Compuestos de imidazoquinolona.

Las composiciones que contienen minerales adecuadas para el uso como coadyuvantes incluyen, sin limitación, sales minerales, por ejemplo, sales de aluminio y sales de calcio. Solo a modo de ejemplo, dichas sales minerales incluyen hidróxidos (por ejemplo, oxihidróxidos, que incluyen hidróxidos de aluminio y oxihidróxidos de aluminio), fosfatos (por ejemplo, hidroxifosfatos y ortofosfatos, que incluyen fosfatos de aluminio, hidroxifosfatos de aluminio, ortofosfatos de aluminio y fosfato de calcio), sulfatos (por ejemplo, sulfato de aluminio), o mezclas de diferentes compuestos minerales. Dichas sales minerales se presentan en cualquier forma adecuada, por ejemplo, en forma de gel, en formas cristalina y amorfa. En ciertas realizaciones, dichas composiciones que contienen minerales se formulan como una partícula de la sal metálica. En ciertas realizaciones, los componentes de las composiciones inmunógenas que se

describen en la presente solicitud son adsorbidos por dichas sales minerales. En ciertas realizaciones, se usa un coadyuvante de hidróxido de aluminio o fosfato de aluminio en las composiciones inmunógenas que aquí se describen. En otras realizaciones, se los antígenos utilizados en una composición inmunógena descripta en la presente solicitud son adsorbidos por dichos coadyuvantes de hidróxido de aluminio o fosfato de aluminio. En ciertas realizaciones, se usa un coadyuvante de fosfato de calcio en las composiciones inmunógenas que se describen en esta solicitud. En otras realizaciones, los antígenos utilizados en una composición inmunógena descripta en esta solicitud son adsorbidos por dichos coadyuvantes de fosfato de calcio.

En ciertas realizaciones, los fosfatos de aluminio se usan como coadyuvantes en las composiciones inmunógenas que se describen en la presente solicitud. En otras realizaciones, se usan fosfatos de aluminio como coadyuvantes en las composiciones inmunógenas que se describen en esta solicitud, donde dichas composiciones incluyen un antígeno de sacárido de *H. influenzae*. En ciertas realizaciones, el coadyuvante es hidroxifosfato de aluminio amorfo con una relación molar de PO_4/Al entre 0,84 y 0,92, incluido en una concentración de 0,6 mg Al^{3+}/ml. En otras realizaciones, se usa la adsorción con una baja dosis de fosfato de aluminio, solo a modo de ejemplo, entre 50 y 100 µg de Al^{3+} por conjugado por dosis. Cuando hay más de un conjugado en una composición, no es necesaria la adsorción de todos los conjugados.

Las emulsiones oleosas adecuadas para el uso como coadyuvantes comprenden, sin limitación, emulsiones de escualeno–agua (tales como MF59 (5% de escualeno, 0,5% de Tween 80 y 0,5% de Span 85, formuladas como partículas submicrónicas utilizando un instrumento microfluidizador), coadyuvante de Freund completo (CFA, por sus siglas en inglés) y coadyuvante de Freund incompleto (IFA, por sus siglas en inglés).

Las saponinas son un grupo heterólogo de esterol glicósidos y glicósidos triterpenoides que se hallan en la corteza, las hojas, los tallos, las raíces y aun en las flores de un amplio rango de especies de plantas. Las formulaciones de saponinas adecuadas para el uso como coadyuvantes incluyen, sin limitación, saponinas de la corteza del árbol Quillaia saponaria Molina, de *Smilax ornata* (sarsaprila), *Gipsofilla paniculata* (velo de novia) y *Saponaria officianalis* (raíz de jabón). En ciertas realizaciones, las formulaciones de saponinas adecuadas para el uso como coadyuvantes incluyen, sin limitación, formulaciones purificadas que incluyen, entre otras, QS7, QS17, QS18, QS21, QH–A, QH–B y QH–C. QS21 se comercializa como STIMULOM™. En otras realizaciones, las formulaciones de saponinas comprenden esteroles, colesteroles y formulaciones lípidas tales como partículas de carácter único formadas por las combinaciones de saponinas y colesteroles denominadas complejos inmunoestimulantes (ISCOM, por sus siglas en inglés). En ciertas realizaciones los ISCOM también incluyen un fosfolípido tal como fosfatidiletanolamina o fosfatidilcolina. Puede usarse cualquier saponina conocida en los ISCOM. En ciertas realizaciones, el ISCOM comprende una o más de QuilA, QHA y QHC. En otras realizaciones, los ISCOM están opcionalmente desprovistos de un detergente adicional.

Los virosomas y las partículas de tipo viral (VLP, por sus siglas en inglés) adecuados para el uso como coadyuvantes incluyen, sin limitación, una o más proteínas de un virus opcionalmente combinado o formulado con un fosfolípido. Dichos virosomas y VLP son generalmente no patógenos, no replicantes y, en general, no contienen ningún genoma viral natural. En ciertas realizaciones, las proteínas virales se producen en forma biotecnológica, mientras que en otras realizaciones, las proteínas virales son aisladas de virus enteros.

Las proteínas virales adecuadas para el uso en virosomas o VLP incluyen, sin limitación, proteínas derivadas del virus de la gripe (tales como HA o NA), del

virus de la hepatitis B (tales como proteínas cápsidas o de núcleo), del virus de la hepatitis E, el virus del sarampión, virus Sindbis, rotavirus, virus de glosopeda, retrovirus, virus de Norwalk, virus de papiloma humano, HIV, fagos de ARN, fagos de Qβ (tales como proteínas de cubierta), fagos de GA, fr–fagos, fagos AP205 y Ti (tales como retrotransposón Ty proteína p1).

Los derivados bacterianos o microbianos adecuados para el uso como coadyuvantes incluyen, sin limitación, derivados bacterianos o microbianos tales como derivados no tóxicos de lipopolisacárido (LPS) enterobacteriano, derivados de lípido A, oligonucleótidos inmunoestimulantes y toxinas ribosilantes de ADP y sus derivados detoxificados. Dichos derivados no tóxicos de LPS incluyen, sin limitación, monofosforilo lípido A (MPL) y MPL 3–O–deacilado (3dMPL). El 3dMPL es una mezcla de monofosforilo lípido A 3 de–O–acilado con 4; 5 ó 6 cadenas aciladas. Otros derivados de LPS no tóxicos incluyen mímicos de monofosforilo lípido A, tales como derivados de aminoalquil glucosaminida fosfato (por ejemplo, RC–529). Los derivados de lípido A incluyen, sin limitación, derivados de lípido A de *Escherichia coli* (por ejemplo, OM–174).

Los oligonucleótidos inmunoestimulantes utilizados como coadyuvantes abarcan, sin limitación, secuencias de nucleótidos que contienen un motivo CpG (una secuencia de dinucleótido que contiene una citosina no metilada ligada por medio de un enlace de fosfato a una guanosina). Dichas secuencias CpG pueden ser de hebra doble o de hebra simple. En ciertas realizaciones, dichas secuencias de nucleótidos son ARN de doble hebra u oligonucleótidos que contienen secuencias palindrómicas o poli(dG). En otras realizaciones, las CpG incluyen análogos/modificaciones de nucleótidos tales como modificaciones de fosforotioato.

En ciertas realizaciones, la secuencia CpG está dirigida a TLR9, y en ciertas realizaciones, el motivo es GTCGTT o TTCGTT. En ciertas realizaciones,

la secuencia CpG es específica para la inducción de una respuesta inmunitaria Th1 tal como, solo a modo de ejemplo, una CpG–A ODN, o en otras realizaciones, la secuencia CpG es más específica para la inducción de una respuesta de células B, tal como, solo a modo de ejemplo, una CpG–B ODN. En ciertas realizaciones, la CpG es una CpG–A ODN.

En ciertas realizaciones, el oligonucleótido CpG está construido de modo que el extremo 5' es accesible para el reconocimiento de receptor. En otras realizaciones, dos secuencias de oligonucleótidos CpG están opcionalmente ligadas en sus extremos 3' para formar "inmunómeros".

Un coadyuvante particularmente útil a base de oligonucleótidos inmunoestimulantes se conoce como IC–31™. En ciertas realizaciones, un coadyuvante utilizado con las composiciones inmunógenas que se describen en la presente solicitud comprende una mezcla de (i) un oligonucleótido (tal como, solo a modo de ejemplo, entre 15–40 nucleótidos) que incluye por lo menos un (y preferentemente, múltiples) motivos CpI (tales como, solo a modo de ejemplo, una citosina ligada a una inosina para formar un dinucleótido); y (ii) un polímero policatiónico, tal como, solo a modo de ejemplo, un oligopéptido (tal como, solo a modo de ejemplo, entre 5–20 aminoácidos) que incluye por lo menos un (y preferentemente, múltiples) secuencias tripeptídicas Lys–Arg–Lys. En ciertas realizaciones, el oligonucleótido es un desoxinucleótido que comprende secuencia 26–mer 5'–$(IC)_{13}$–3'. En otras realizaciones, el polímero policatiónico es un péptido que comprende secuencia de aminoácidos 11–mer KLKLLLLLKLK.

En ciertas realizaciones, las toxinas ribosilantes de ADP bacterianas y sus derivados detoxificados se usan como coadyuvantes en las composiciones inmunógenas que se describen en la presente solicitud. En ciertas realizaciones, dichas proteínas derivan de *E. coli* (enterotoxina lábil al calor de *E. coli* "LT"), cólera ("CT"), o tos ferina ("PT"). En otras realizaciones, la toxina o el toxoide es

se presenta en la forma de una holotoxina, que comprende tanto la subunidad A como la B. En otras realizaciones, la subunidad A contiene una mutación detoxificante, mientras que la subunidad B no está mutada. En otras realizaciones, el coadyuvante es una mutante LT detoxificada tal como LT–K63, LT–R72 y LT–G192.

Los inmunomoduladores humanos adecuados para el uso como coadyuvantes abarcan, sin limitación, citoquinas, tales como, solo a modo de ejemplo, interleuquinas (IL–1, IL–2, IL–4, IL–5, IL–6, IL–7, IL–12), interferones (tales como, solo a modo de ejemplo, interferón–γ), factor estimulante de colonia de macrófagos y factor de necrosis tumoral.

Los bioadhesivos y mucoadhesivos utilizados como coadyuvantes en las composiciones inmunógenas que se describen en la presente solicitud incluyen, sin limitación, microesferas de ácido hialurónico esterificado, y derivados entrecruzados de ácido poli(acrílico), polivinil alcohol, polivinilpirolidona, polisacáridos y carboximetilcelulosa. En ciertas realizaciones, se usan quitosano y sus derivados como coadyuvantes, en las composiciones de vacuna que se describen en la presente solicitud.

Las micropartículas adecuadas para el uso como coadyuvantes comprenden, sin limitación, micropartículas formadas a partir de materiales que son biodegradables y no tóxicos (por ejemplo, un poli(ácido .alfa.–hidroxi), un ácido polihidroxibutírico, un poliortoéster, un polianhídrido, una policaprolactona, etc.), con poli(láctido–co–glicólido). En ciertas realizaciones, dichas micropartículas se tratan de manera de poseer una superficie cargada negativamente (por ejemplo, con SDS) o una superficie cargada positivamente (por ejemplo, con un detergente catiónico, tal como CTAB). Las micropartículas adecuadas para el uso como coadyuvantes tienen un diámetro de partícula de alrededor de 100 nm a alrededor de 150 μm de diámetro. En ciertas realizaciones,

el diámetro de partícula es de alrededor de 200 nm a alrededor de 30 μm, y en otras realizaciones, el diámetro de partícula es de aproximadamente 500 nm a 10 μm.

Las formulaciones de polioxietileno éter y polioxietileno éster adecuadas para el uso como coadyuvantes incluyen, sin limitación, surfactantes de polioxietileno sorbitano éster en combinación con un octoxinol, y surfactantes de polioxietileno alquil éteres o éster en combinación con por lo menos un surfactante no iónico adicional, tal como un octoxinol. En ciertas realizaciones, los polioxietileno éteres se seleccionan de polioxietileno–9–lauril éter (lauret 9), polioxietileno–9–esteoril éter, polioxiteleno–8–esteoril éter, polioxietileno–4–lauril éter, polioxietileno–35–lauril éter y polioxietileno–23–lauril éter.

Los péptidos de muramilo adecuados para el uso como coadyuvantes incluyen, sin limitación, N–acetil–muramil–L–treonil–D–isoglutamina (thr–MDP), N–acetil–normuramil–L–alanil–D–isoglutamina (nor–MDP) y N–acetilmuramil–L–alanil–D–isoglutaminil–L–alanina–2–(1'–2'–dipalmitoil–s–n–glicero–3–hidroxifosforiloxi)–etilamina (MTP–PE).

En ciertas realizaciones, se incluyen uno o más compuestos de la Fórmula (I) utilizados como potenciador inmunitario, en las composiciones que tienen combinaciones de uno o más de los coadyuvantes identificados con anterioridad. Dichas combinaciones abarcan, sin limitación:

(1) una saponina y una emulsión de aceite en agua;

(2) una saponina (por ejemplo, QS21) + un derivado de LPS no tóxico (por ejemplo, 3dMPL);

(3) una saponina (por ejemplo, QS21) + un derivado de LPS no tóxico (por ejemplo, 3dMPL) + un colesterol;

(4) una saponina (por ejemplo, QS21) + 3dMPTL + IL–12 (que opcionalmente incluye un esterol);

(5) combinaciones de 3dMPL con, por ejemplo, QS21 y/o emulsiones de aceite en agua;

(6) SAF, que contiene 10% de escualano, 0,4% de Tween 80.TM., 5% de polímero de bloques plurónico L121 y thr–MDP, microfluidizado en una emulsión submicrónica o sometido a torbellino para generar una emulsión de tamaño de partícula mayor;

(7) un sistema coadyuvante RIBI™ (RAS), (Ribi Immunochem) que contiene 2% de escualeno, 0,2% de Tween 80, y uno o más componentes de la pared celular bacteriana del grupo que consiste en monofosforilípido A (MPL), trehalosa dimicolato (TDM) y esqueleto de la pared celular (CWS), preferentemente, MPL + CWS (Detox.TM.); y

(8) una o más sales minerales (tales como sal de aluminio) + un derivado no tóxico de LPS (tal como 3dMPL).

En otras realizaciones, las combinaciones coadyuvantes utilizadas en las combinaciones inmunógenas proporcionadas en la presente solicitud incluyen combinaciones de coadyuvantes Th1 y Th2 tales como, solo a modo de ejemplo, CpG y alumbre o resiquimod y alumbre.

En ciertas realizaciones, las composiciones inmunógenas que se proveen en la presente solicitud producen tanto una respuesta inmunitaria celular como una respuesta inmunitaria humoral. En otras realizaciones, la respuesta inmunitaria induce anticuerpos de larga duración (por ejemplo, neutralizantes) y una inmunidad celular que responde rápidamente con la exposición al agente infeccioso.

En general, se consideran necesarios dos tipos de células T, las células CD4 y CD8, para iniciar o mejorar la inmunidad celular y la inmunidad humoral. Las células T CD8 pueden expresar un correceptor CD8 y, comúnmente, se denominan linfocitos T citotóxicos (CTL). Las células T CD8 pueden reconocer

antígenos exhibidos en moléculas MHC Clase I, o interactuar con ellos.

Las células T CD4 expresan un correceptor CD4, y comúnmente, se denominan células cooperadoras T. Las células T CD4 pueden reconocer péptidos antígenos ligados a moléculas MHC clase II. Con la interacción con una molécula MHC clase II, las células CD4 pueden secretar factores tales como citoquinas. Estas citoquinas secretadas pueden activar células B, células T citotóxicas, macrófagos y otras células que participan en una respuesta inmunitaria. Las células T cooperadoras o las célula CD4+ además pueden dividirse en dos subclases funcionalmente distintas: el fenotipo TH1 y el fenotipo TH2 que difieren en su función efectora y de citoquina.

Las células activadas TH1 mejoran la inmunidad celular (lo que incluye un incremento en la producción de CTL específico de antígeno), y por lo tanto, son de particular valor en la respuesta a infecciones intracelulares. Las células TH1 activadas pueden secretar uno o más de IL–2, IFN–γ y TNF–β. Una respuesta inmunitaria de TH1 puede lograr reacciones inflamatorias locales mediante la activación de macrófagos, linfocitos citolíticos naturales y células T citotóxicas CD8 (CTL). Una respuesta inmunitaria TH1 además puede actuar para expandir la respuesta inmunitaria mediante la estimulación del crecimiento de células B y T con IL–12. Las células B estimuladas por TH1 pueden secretar IgG2a.

Las células TH2 activadas mejoran la producción de anticuerpos, y por lo tanto, son de valor en la respuesta a las infecciones extracelulares. Las células TH2 activadas pueden secretar uno o más de IL–4, IL–5, IL–6 e IL–10. Una respuesta inmunitaria TH2 puede lograr la producción de IgG1, IgE, IgA y células B de memoria para la futura protección.

Una respuesta inmunitaria mejorada puede incluir una o más de una respuesta inmunitaria TH1 mejorada y una respuesta inmunitaria TH2 mejorada.

Una respuesta inmunitaria TH1 puede incluir uno o más de un incremento

en CTL, un incremento en una o más de las citoquinas asociadas con una respuesta inmunitaria TH1 (tal como IL–2, IFN–γ y TNF–β), un incremento en los macrófagos activados, un incremento en la actividad de NK, o un incremento en la producción de IgG2a. Preferentemente, la mejor respuesta inmunitaria TH1 incluirá un incremento en la producción de IgG2a.

Los coadyuvantes de TH1 pueden usarse para producir una respuesta inmunitaria TH1. Un coadyuvante de TH1, en general, producirá mayores niveles de producción de IgG2a en relación con la inmunización del antígeno sin coadyuvante. Los coadyuvantes de TH1 adecuados para el uso en las composiciones inmunógenas que se proporcionan en la presente solicitud incluyen, sin limitación, formulaciones de saponinas, virosomas y partículas de tipo viral, derivados no tóxicos de lipopolisacárido enterobacteriano (LPS), oligonucleótidos inmunoestimulantes. En ciertas realizaciones, los oligonucleótidos inmunoestimulantes utilizados como coadyuvantes de TH1 en las composiciones inmunógenas que se proveen en esta solicitud contienen un motivo CpG.

Una respuesta inmunitaria TH2 puede incluir uno o más de un incremento en una o más de las citoquinas asociadas con una respuesta inmunitaria TH2 (por ejemplo, IL–4, IL–5, IL–6 e IL–10), o un incremento en la producción de IgG1, IgE, IgA y células B de memoria. Preferentemente, la respuesta inmunitaria TH2 incluirá un incremento en la producción de IgG1.

Los coadyuvantes de TH2 pueden usarse a fin de producir una respuesta inmunitaria TH2. Un coadyuvante de TH2, en general, producirá mayores niveles de producción de IgG1, en relación con la inmunización del antígeno sin coadyuvante. Los coadyuvantes de TH2 adecuados para el uso en composiciones inmunógenas proporcionadas en la presente solicitud incluyen, sin limitación, composiciones que contienen minerales, emulsiones oleosas y toxinas

ribosilantes de ADP y sus derivados detoxificados. En ciertas realizaciones, las composiciones que contienen minerales utilizadas como coadyuvantes de TH2 en las composiciones inmunógenas que se proveen en esta solicitud son sales de aluminio.

En ciertas realizaciones, las composiciones inmunógenas que se proporcionan en la presente solicitud incluyen un coadyuvante de TH1 y un coadyuvante de TH2. En otras realizaciones, dichas composiciones producen una respuesta TH1 mejorada y una respuesta TH2 mejorada, por ejemplo, un incremento en la producción tanto de IgG1 como de IgG2 en relación con la inmunización sin un coadyuvante. Aun en otras realizaciones, dichas composiciones que comprenden una combinación de un coadyuvante de TH1 y un coadyuvante de TH2 producen una mejor respuesta inmunitaria TH1 y/o una mejor respuesta inmunitaria TH2, en relación con la inmunización con un solo coadyuvante (es decir, en relación con la inmunización con un coadyuvante de TH1 solo, o la inmunización con un coadyuvante de TH2 solo).

En ciertas realizaciones, la respuesta inmunitaria es una de una respuesta inmunitaria TH1 y una respuesta inmunitaria TH2, o ambas. En otras realizaciones, la respuesta inmunitaria proporciona una o ambas de una respuesta TH1 mejorada y una respuesta TH2 mejorada.

En ciertas realizaciones, la respuesta inmunitaria mejorada es una o ambas de una respuesta inmunitaria sistémica y una respuesta inmunitaria mucosal. En otras realizaciones, la respuesta inmunitaria proporciona una o ambas de una mejor respuesta inmunitaria sistémica y una mejor respuesta inmunitaria mucosal. En ciertas realizaciones, la respuesta inmunitaria mucosal es una respuesta inmunitaria TH2. En ciertas realizaciones, la respuesta inmunitaria mucosal incluye un incremento en la producción de IgA.

En ciertas realizaciones, las composiciones inmunógenas proporcionadas

en la presente solicitud se usan como vacunas, donde dichas composiciones incluyen una cantidad inmunológicamente eficaz de uno o más antígenos.

Los antígenos para el uso con las composiciones inmunógenas proporcionadas en la presente solicitud incluyen, sin limitación, uno o más de los siguientes antígenos expuestos a continuación, o antígenos derivados de uno o más de los patógenos expuestos a continuación.

Antígenos bacterianos.

Los antígenos bacterianos adecuados para el uso como composiciones inmunógenas proporcionadas en la presente solicitud incluyen, sin limitación, proteínas, polisacáridos, lipopolisacáridos y vesículas de membranas externas aisladas, purificadas o derivadas de una bacteria. En ciertas realizaciones, los antígenos bacterianos incluyen lisados bacterianos y formulaciones de bacterias inactivas. En ciertas realizaciones, los antígenos bacterianos se producen mediante la expresión recombinada. En ciertas realizaciones, los antígenos bacterianos incluyen epítopos expuestos sobre la superficie de las bacterias durante por lo menos una etapa de su ciclo de vida. Los antígenos bacterianos, preferentemente, se conservan a través de múltiples serotipos. En ciertas realizaciones, los antígenos bacterianos incluyen antígenos derivados de una o más de las bacterias expuestas a continuación, al igual que los ejemplos de antígenos específicos identificados debajo.

Neisseria meningitidis: los antígenos de *Meningitidis* incluyen, sin limitación, proteínas sacáridos (que incluyen un polisacárido, oligosacárido, lipooligosacárido o lipopolisacárido), o vesículas de membranas externas purificadas o derivadas de serogrupo de *N. meningitides* tales como A, C, W135, Y, X y/o B. En ciertas realizaciones, los antígenos de proteínas de *meningitides* pueden seleccionarse de adhesiones, autotransportadores, toxinas, proteínas de

adquisición de Fe y proteínas asociadas con membranas (preferentemente, proteína de membrana externa integral).

Streptococcus pneumoniae: los antígenos de *Streptococcus pneumoniae* incluyen, sin limitación, un sacárido (que comprende un polisacárido o un oligosacárido) y/o proteína de *Streptococcus pneumoniae*. El sacárido puede ser un polisacárido que tiene un tamaño que surge durante la purificación del sacárido de las bacterias, o puede ser un oligosacárido logrado mediante la fragmentación de dicho polisacárido. En el producto 7–valente PREVNAR™, por ejemplo, 6 de los sacáridos se presentan como polisacáridos intactos, mientras que uno (el serotipo 18C) se presenta como un oligosacárido. En ciertas realizaciones, los antígenos de sacáridos se seleccionan de uno o más de los siguientes serotipos pneumocócicos: 1; 2; 3; 4; 5; 6A; 6B; 7F; 8; 9N; 9V; 10A; 11A; 12F; 14; 15B; 17F; 18C, 19A; 19F; 20; 22F; 23F; y/o 33F. Una composición inmunógena puede incluir múltiples serotipos, por ejemplo, 2; 3; 4; 5; 6; 7; 8; 9; 10; 11; 12; 13; 14; 15; 16; 17; 18; 19; 20; 21; 22; 23 o más serotipos. Se conocen ya en el arte las combinaciones de conjugados 7–valentes; 9–valentes; 10–valentes; 11–valentes y 13–valentes, al igual que una combinación no conjugada 23–valente. Por ejemplo, una combinación 10–valente puede incluir sacárido de los serotipos 1; 4; 5; 6B; 7F; 9V; 14; 18C; 19F y 23F. Una combinación 11–valente puede incluir además sacárido del serotipo 3. Una combinación 12–valente puede añadir a la mezcla 10–valente: los serotipos 6A y 19A; 6A y 22F; 19A y 22F; 6A y 15B; 19A y 15B; r 22F y 15B. Una combinación 13–valente puede agregar a la mezcla 11–valente: los serotipos 19A y 22F; 8 y 12F; 8 y 15B; 8 y 19A; 8 y 22F; 12F y 15B; 12F y 19A; 12F y 22F; 15B y 19A; 15B y 22F. etc. En ciertas realizaciones, los antígenos de proteínas pueden seleccionarse de una proteína identificada en los documentos WO 98/18931; WO 98/18930; Patente de los Estados Unidos Nro. 6.699.703; Patente de los Estados Unidos Nro. 6.800.744; WO 97/43303; WO

97/37026; WO 02/079241; WO 02/34773; WO 00/06737; WO 00/06738; WO 00/58475; WO 2003/082183; WO 00/37105; WO 02/22167; WO 02/22168; WO 2003/104272; WO 02/08426; WO 01/12219; WO 99/53940; WO 01/81380; WO 2004/092209; WO 00/76540; WO 2007/116322; las referencias de LeMieux *et al.*: *Infect. Imm.* (2006) 74: 2453–2456; Hosquins *et al.*, *J. Bacteriol.* (2001) 183: 5709–5717; Adamou *et al.*: *Infect. Immun.* (2001) 69 (2): 949–958, Briles *et al.*: *J. Infect. Dis.* (2000) 182: 1694–1701; Talkington *et al.*: *Microb. Pathog.* (1996) 21 (1): 17–22, Bethe *et al.*: *FEMS Microbiol. Lett.* (2001) 205 (1): 99–104; Brown *et al.*: *Infect. Immun.* (2001) 69: 6702–6706; Whalen *et al.*: *FEMS Immunol. Med. Microbiol.* (2005) 43: 73–80; Jomaa *et al.*: *Vaccine* (2006) 24 (24): 5133–5139. En otras realizaciones, las proteínas de *Streptococcus pneumoniae* pueden seleccionarse de la familia de polihistidina Triad (PhtX), la familia de proteínas de unión de colina (CbpX), truncados de CbpX, la familia LytX, truncados de LytX, proteínas quiméricas de truncado CbpX–truncado LytX, pneumolisina (Ply), PspA, PsaA, Spl28, SplOl, Spl30, Spl25, Spl33, subunidades pilosas pneumocócicas.

Streptococcus pyogenes (Streptococcus Grupo A*)*. Los antígenos de *Streptococcus* Grupo A incluyen, sin limitación, una proteína identificada en el documento WO 02/34771 o WO 2005/032582 (que incluye GAS 40), fusiones de fragmentos de proteínas GAS M (que incluyen aquellas descriptas en el documento WO 02/094851, y en la referencia de Dale: *Vaccine* (1999) 17: 193–200, y Dale: *Vaccine* 14 (10): 944–948), proteína de unión de fibronectina (Sfb1), proteína hemoasociada estreptocócica (Shp) y estreptolisina S (SagA).

Moraxella catarrhalis. Los antígenos de *Moraxella* incluyen, sin limitación, antígenos identificados en los documentos WO 02/18595 y WO 99/58562, antígenos de proteínas de membranas externas (HMW–OMP), antígeno C y LPS.

Bordetella pertussis. Los antígenos de la tos ferina incluyen, sin limitación, holotoxina de tos ferina (PT) y hemaglutinina filamentosa (FHA) de *B. pertussis*, opcionalmente, además, en combinación con pertactina y/o aglutinógenos 2 y 3.

Burkholderia. Los antígenos de *Burkholderia* incluyen, sin limitación, *Burkholderia malei*, *Burkholderia pseudomalei* y *Burkholderia cepacia*.

Staphylococcus aureus. Los antígenos de *Staph aureus* incluyen, sin limitación, polisacárido y/o proteína de *S. aureus*. Los polisacáridos de *S. aureus* incluyen, sin limitación, polisacáridos capsulares de tipo 5 y tipo 8 (CP5 y CP8), opcionalmente conjugados con exotoxina A de *Pseudomonas aeruginosa* recombinada no tóxica, tal como StaphVAX™, polisacáridos tipo 336 (336PS), adhesiones intracelulares de polisacáridos (PIA, por sus siglas en inglés, también conocidas como PNAG). Las proteínas de *S. aureus* incluyen, sin limitación, antígenos derivados de proteínas de superficie, invasinas (leucocidina, quinasas, hialuronidasa), factores de superficie que inhiben el rodeo fagocítico (cápsula, Proteína A), carotenoides, producción de catalasa, Proteína A, coagulasa, factor de coagulación, y/o toxinas que dañan la membrana (opcionalmente detoxificadas) que lisan membranas celulares eucariotas (hemolisinas, leucotoxina, leucocidina). En ciertas realizaciones, los antígenos de *S. aureus* pueden seleccionarse de una proteína identificada en los documentos WO 02/094868, WO 2008/019162, WO 02/059148, WO 02/102829, WO 03/011899, WO 2005/079315, WO 02/077183, WO 99/27109, WO 01/70955, WO 00/12689, WO 00/12131, WO 2006/032475, WO 2006/032472, WO 2006/032500, WO 2007/113222, WO 2007/113223, WO 2007/113224. En otras realizaciones, los antígenos de *S. aureus* pueden seleccionarse de IsdA, IsdB, IsdC, SdrC, SdrD, SdrE, ClfA, ClfB, SasF, SasD, SasH (AdsA), Spa, EsaC, EsxA, EsxB, Emp, HlaH35L, CP5, CP8, PNAG, 336PS.

Staphylococcus epidermis. Los antígenos de *S. epidermidis* incluyen, sin limitación, antígeno asociado a cieno (SAA, por sus siglas en inglés).

Clostridium tetani (tétano). Los antígenos del tétano incluyen, sin limitación, toxoide de tétanos (TT). En ciertas realizaciones, dichos antígenos se usan como una proteína portadora en conjunto con las composiciones inmunógenas proporcionadas en la presente solicitud, o conjugadas con dichas composiciones.

Clostridium perfringens. Los antígenos incluyen, sin limitación, toxina Epsilon de *Clostridium perfringen.*

Clostridium botulinums (botulismo). Los antígenos del botulismo incluyen, sin limitación, aquellos derivados de *C. botulinum.*

Cornynabacterium diphtheriae (difteria). Los antígenos de la difteria incluyen, sin limitación, toxina de difteria, preferentemente, detoxificada, tal como CRM_{197}. Los antígenos adicionales capaces de modular o inhibir la ribosilación de ADP o de asociarse a dicha ribosilación se contemplan para la combinación, coadministración o conjugación con las composiciones inmunógenas proporcionadas en la presente solicitud. En ciertas realizaciones, los toxoides de difteria se usan como proteínas portadoras.

Haemofilus influenzae B (Hib). Los antígenos de Hib incluyen, sin limitación, un antígeno de sacárido de Hib.

Pseudomonas aeruginosa. Los antígenos de *Pseudomonas* incluyen, sin limitación, endotoxina A, proteína Wzz, LPS de *P. aeruginosa*, LPS aislado de PAO1 (setotipo O5), y/o proteínas de membrana externa, que incluyen proteínas de membrana externa F (OprF).

Legionella pneumophila. Los antígenos bacterianos derivados de *Legionella pneumophila.*

Coxiella burnetii. Los antígenos bacterianos derivados de *Coxiella burnetii.*

Brucella. Los antígenos bacterianos derivados de *Brucella*, que incluyen, sin limitación, *B. abortus, B. canis, B. melitensis, B. neotomae, B. ovis, B. suis* y *B. pinnipediae.*

Francisella. Los antígenos bacterianos derivados de *Francisella*, que incluyen, sin limitación, *F. novicida, F. philomiragia* y *F. tularensis.*

Streptococcus agalactiae (Streptococcus Grupo B*)*. Los antígenos de *Streptococcus* Grupo B incluyen, sin limitación, una proteína o un antígeno de sacárido identificados en los documentos WO 02/34771, WO 03/093306, WO 04/041157, o WO 2005/002619 (que incluyen proteínas GBS 80, GBS 104, GBS 276 y GBS 322, y que incluyen antígenos de sacáridos derivados de los serotipos Ia, Ib, Ia/c, II, III, IV, V, VI, VII y VIII).

Neiserria gonorrhoeae. Los antígenos de gonorrea incluyen, sin limitación, proteína Por (o porina), tal como PorB (ver la referencia de Zhu *et al.*: *Vaccine* (2004) 22: 660–669), una proteína de unión de transferencia, tal como TbpA y TbpB (ver la referencia de Price *et al.*: *Infection and Immunity* (2004) 71 (1): 277–283), una proteína de opacidad (tal como Opa), una proteína de modificación de reducción (Rmp, por sus siglas en inglés), y preparaciones de vesícula de membrana externa (OMV) (ver la referencia de Plante *et al.*: *J. Infectious Disease* (2000) 182: 848–855); ver además, por ejemplo, los documentos WO 99/24578, WO 99/36544, WO 99/57280, WO 02/079243).

Chlamydia trachomatis. Los antígenos de *Chlamydia trachomatis* incluyen, sin limitación, antígenos derivados de los serotipos A, B, Ba y C (agentes de tracoma, una causa de ceguera), serotipos L_1, L_2 y L_3 (asociados con linfogranuloma venéreo), y serotipos, D–K. En ciertas realizaciones, los antígenos de tracoma de clamidia incluyen, sin limitación, un antígeno identificado en los documentos WO 00/37494, WO 03/049762, WO 03/068811, o WO 05/002619, que incluye PepA (CT045), LcrE (CT089), ArtJ (CT381), DnaK (CT396), CT398,

de tipo OmpH (CT242), L7/L12 (CT316), OmcA (CT444), AtosS (CT467), CT547, Eno (CT587), HrtA (CT823) y MurG (CT761).

Treponema pallidum (sífilis). Los antígenos de sífilis incluyen, sin limitación, el antígeno TmpA.

Haemophilus ducreyi (que causa chancro blando). Los antígenos de *Ducreyi* incluyen, sin limitación, proteína de membrana externa (DsrA).

Enterococcus faecalis o *Enterococcus faecium.* Los antígenos incluyen, sin limitación, una repetición de trisacárido u otros antígenos derivados de *Enterococcus*.

Helicobacter pilory. Los antígenos de *H pilory* incluyen, sin limitación, Cag, Vac, Nap, HopX, HopY y antígeno de ureasa.

Staphylococcus saprophyticus. Los antígenos incluyen, sin limitación, la hemaglutinina de 160 kDa del antígeno de *S. saprophyticus*.

Yersinia enterocolitica. Los antígenos incluyen, sin limitación, LPS.

E. coli. Los antígenos de *E. coli* pueden derivar de *E. coli* enterotoxigénico (ETEC), *E. coli* enteroagregado (EAggEC), *E. coli* difusamente adherente (DAEC), *E. coli* enteropatógeno (EPEC), *E. coli* patógeno extraintestinal (ExPEC) y *E. coli* enterohemorrágico (EHEC). Los antígenos de ExPEC incluyen, sin limitación, factor de colonización accesoria (orf3526), orf353, proteína de dominio de tipo Ig bacteriano (grupo 1) (orf405), orf1364, transportador de afluencia de lipoproteína–factor de membrana externa de la familia NodT (orf1767), gspK (orf3515), gspJ (orf3516), receptor de sideróforo dependiente de tonB (orf3597), proteína fimbrial (orf3613), upec–948, upec–1232, precursor de cadena A de la proteína fimbrial de tipo 1 (upec–1875), homólogo de yap H (upec–2820) y hemolisina A (recp–3768).

Bacillus anthracis (ántrax). Los antígenos de *B. anthracis* incluyen, sin limitación, componentes A (factor letal (LF, por sus siglas en inglés) y factor de edema (EF, por sus siglas en inglés)), donde ambos pueden compartir un

componente B común conocido como antígeno protector (PA, por sus siglas en inglés). En ciertas realizaciones, los antígenos de *B. anthracis* son opcionalmente detoxificados.

*Yersinia pestis (*plaga*)*. Los antígenos de plaga incluyen, sin limitación, antígeno capsular F1, LPS, antígeno V de *Yersinia pestis*.

Mycobacterium tuberculosis. Los antígenos de tuberculosis incluyen, sin limitación, lipoproteínas, LPS, antígenos de BCG (bacilo de Calmette y Guérin), una proteína de fusión del antígeno 85B (Ag85B), ESAT–6 opcionalmente formulado en vesículas lípidas catiónicas, antígenos asociados con isocitrato dehidrogenasa de *Mycobacterium tuberculosis* (Mtb) y antígenos MPT51.

Rickettsia. Los antígenos incluyen, sin limitación, proteínas de membrana externa, que incluyen la proteína de membrana externa A y B (OmpB), LPS y antígeno de proteína de superficie (SPA, por sus siglas en inglés).

Listeria monocytogenes. Los antígenos incluyen, sin limitación, aquellos derivados de *Listeria monocytogenes*.

Chlamydia pneumoniae. Los antígenos incluyen, sin limitación, aquellos identificados en el documento WO 02/02606.

Vibrio cholerae. Los antígenos incluyen, sin limitación, antígenos de proteinasa, LPS, en particular, lipopolisacáridos de *Vibrio cholerae* II, polisacáridos específicos de O O1 Inaba, *V. cholera* O139, antígenos de vacuna IEM108 y toxina *Zonula occludens* (Zot).

Salmonella typhi (fiebre tifoidea). Los antígenos incluyen, sin limitación, polisacáridos capsulares, preferentemente, conjugados (Vi, es decir, vax–TyVi).

Borrelia burgdorferi (enfermedad de Lyme). Los antígenos incluyen, sin limitación, lipoproteínas (tales como OspA, OspB, Osp C y Osp D), otras proteínas de superficie tales como proteínas relacionadas con OspE (Erps), proteínas de unión de decorina (tales como DbpA) y proteínas antigénicamente variables VI,

tales como antígenos asociados con P39 y P13 (una proteína de membrana integral), proteína de variación antigénica VlsE.

Porphyromonas gingivalis. Los antígenos incluyen, sin limitación, proteína de membrana externa de *P. gingivalis* (OMP).

Klebsiella. Los antígenos incluyen, sin limitación, una OMP, que incluye OMP A, o un polisacárido opcionalmente conjugado con toxoide de tétano.

Otros antígenos bacterianos utilizados en las composiciones inmunógenas proporcionadas en la presente solicitud incluyen, sin limitación, antígenos capsulares, antígenos de polisacáridos o antígenos de proteínas de cualquiera de los anteriores. Otros antígenos bacterianos utilizados en las composiciones inmunógenas proporcionadas en la presente solicitud incluyen, sin limitación, una preparación de vesículas de membrana externa (OMV, por sus siglas en inglés). Asimismo, otros antígenos bacterianos utilizados en las composiciones inmunógenas proporcionadas en la presente solicitud incluyen, sin limitación, versiones vivas, atenuadas o purificadas de cualquiera de las bacterias mencionadas con anterioridad. En ciertas realizaciones, los antígenos bacterianos utilizados en las composiciones inmunógenas que se proveen en la presente solicitud derivan de bacterias Gram negativas, mientras que en otras realizaciones, derivan de bacterias Gram positivas. En ciertas realizaciones, lo antígenos bacterianos utilizados en las composiciones inmunógenas que se proveen en la presente solicitud derivan de bacterias aeróbicas, mientras que en otras realizaciones, derivan de bacterias anaeróbicas.

En ciertas realizaciones, cualquiera de los sacáridos derivados de bacterias (polisacáridos, LPS, LOS u oligosacáridos) se conjuga con otro agente o antígeno, tal como una proteína portadora (por ejemplo, CRM_{197}). En ciertas realizaciones, dichas conjugaciones son conjugaciones directas efectuadas mediante la aminación reductora de porciones carbonilo en el sacárido a grupos

amino en la proteína. En otras realizaciones, los sacáridos se conjugan a través de un conector, tal como con succinamida u otras uniones proporcionadas en las referencias tituladas *Bioconjugate Techniques,* 1996, y *CRC, Chemistry of Protein Conjugation and Cross–Linking*, 1993.

En ciertas realizaciones útiles para el tratamiento o la prevención de la infección de *Neisseria* y enfermedades y trastornos relacionados, las proteínas recombinadas de *N. meningitidis* para el uso en las composiciones inmunógenas proporcionadas en esta solicitud pueden hallarse en los documentos WO 99/24578, WO 99/36544, WO 99/57280, WO 00/22430, WO 96/29412, WO 01/64920, WO 03/020756, WO 2004/048404 y WO 2004/032958. Dichos antígenos pueden usarse solos o en combinaciones. Cuando se combinan múltiples proteínas purificadas, entonces es útil el uso de una mezcla de 10 o menos (por ejemplo, 9; 8; 7; 6; 5; 4; 3; 2) antígenos purificados.

Una combinación particularmente útil de antígenos para el uso en las composiciones inmunógenas proporcionadas en la presente solicitud se revela en la referencia de Giuliani *et al.* (2006): *Proc. Natl. Acad. Sci. U. S. A.* 103 (29): 10834–9 y en el documento WO 2004/032958, y por lo tanto, una composición inmunógena puede incluir 1; 2; 3; 4; ó 5 de: (1) una proteína 'NadA' (aka GNA1994 y NMB1994); (2) una proteína 'fHBP' (aka '741', LP2086, GNA1870 y NMB1870); (3) una proteína '936' (aka GNA2091 y NMB2091); (4) una proteína '953' (aka GNA1030 y NMB1030); y (5) una proteína '287' (aka GNA2132 y NMB2132). Otras combinaciones de antígenos posibles pueden comprender una proteína de unión de transferrina (por ejemplo, TbpA y TbpB) y un antígeno Hsf. Otros antígenos purificados posibles para el uso en las composiciones inmunógenas proporcionadas en la presente solicitud incluyen proteínas que comprenden una de los siguientes secuencias de aminoácidos: SEC. ID. NRO.: 650 de WO 99/24578; SEC. ID. NRO.: 878 de WO 99/24578; SEC. ID. NRO.: 884

de WO 99/24578; SEC. ID. NRO.: 4 de WO 99/36544; SEC. ID. NRO.: 598 de WO 99/57280; SEC. ID. NRO.: 818 de WO 99/57280; SEC. ID. NRO.: 864 de WO 99/57280; SEC. ID. NRO.: 866 de WO 99/57280; SEC. ID. NRO.: 1196 de WO 99/57280; SEC. ID. NRO.: 1272 de WO 99/57280; SEC. ID. NRO.: 1274 de WO 99/57280; SEC. ID. NRO.: 1640 de WO 99/57280; SEC. ID. NRO.: 1788 de WO 99/57280; SEC. ID. NRO.: 2288 de WO 99/57280; SEC. ID. NRO.: 2466 de WO 99/57280; SEC. ID. NRO.: 2554 de WO 99/57280; SEC. ID. NRO.: 2576 de WO 99/57280; SEC. ID. NRO.: 2606 de WO 99/57280; SEC. ID. NRO.: 2608 de WO 99/57280; SEC. ID. NRO.: 2616 de WO 99/57280; SEC. ID. NRO.: 2668 de WO 99/57280; SEC. ID. NRO.: 2780 de WO 99/57280; SEC. ID. NRO.: 2932 de WO 99/57280; SEC. ID. NRO.: 2958 de WO 99/57280; SEC. ID. NRO.: 2970 de WO 99/57280; SEC. ID. NRO.: 2988 de WO 99/57280 (cada una de las secuencias de aminoácidos precedentes se incorpora en la presente solicitud a modo de referencia del documento citado), o un polipéptido que comprende una secuencia de aminoácidos que: (a) tiene 50% o más de identidad (por ejemplo, 60%, 70%, 80%, 90%, 95%, 99% o más) con respecto a dichas secuencias; y/o (b) comprende un fragmento de por lo menos n aminoácidos consecutivos de dichas secuencias, donde n es 7 o más (por ejemplo, 8; 10; 12; 14; 16; 18; 20; 25; 30; 35; 40; 50; 60; 70; 80; 90; 100; 150; 200; 250 o más). Los fragmentos preferidos para (b) comprenden un epítopo de la secuencia pertinente. Pueden incluirse más de uno (por ejemplo, 2; 3; 4; 5; 6) de estos polipéptidos en las composiciones inmunógenas.

El antígeno fHBP se encuentra en tres variantes distintas (WO 2004/048404). Una vacuna de serogrupo de *N. meningitidis* sobre la base de las composiciones inmunógenas reveladas en la presente solicitud, que utiliza uno de los compuestos revelados en esta solicitud, puede incluir una sola variante fHBP, si bien será útil incluir una fHBP de cada una de dos variantes, o de las tres

variantes. En consecuencia, la composición inmunógena puede incluir una combinación de dos o tres fHBP purificados diferentes, seleccionados de: (a) una primera proteína, que comprende una secuencia de aminoácidos que tiene por lo menos un % a de identidad de secuencia con respecto a SEC. ID. NRO.: 1, o que comprende una secuencia de aminoácidos que consiste en un fragmento de por lo menos x aminoácidos contiguos de SEC. ID. NRO.: 1; (b) una segunda proteína, que comprende una secuencia de aminoácidos que tiene por lo menos un % b de identidad de secuencia con respecto a SEC. ID. NRO.: 2 o que comprende una secuencia de aminoácidos que consiste en un fragmento de por lo menos y aminoácidos contiguos de SEC. ID. NRO.: 2; y/o (c) una tercera proteína, que comprende una secuencia de aminoácidos que tiene por lo menos un % c de identidad de secuencia con respecto a SEC. ID. NRO.: 3 o que comprende una secuencia de aminoácidos que consiste en un fragmento de por lo menos z aminoácidos contiguos de SEC. ID. NRO.: 3.

SEC. ID. NRO.: 1.
VAADIGAGLADALTAPLDHKDKGLQSLTLDQSVRKNEKLKLAAQGAEKTYGN
GDSLNTGKLKNDKVSRFDFIRQIEVDGQLITLESGEFQVYKQSHSALTAFQTEQI
QDSEHSGKMVAKRQFRIGDIAGEHTSFDKLPEGGRATYRGTAFGSDDAGGKLT
YTIDFAAKQGNGKIEHLKSPELNVDLAAADIKPDGKRHAVISGSVLYNQAEKGS
YSLGIFGGKAQEVAGSAEVKTVNGIRHIGLAAKQ

SEC. ID. NRO.: 2.
VAADIGAGLADALTAPLDHKDKSLQSLTLDQSVRKNEKLKLAAQGAEKTYGN
GDSLNTGKLKNDKVSRFDFIRQIEVDGQLITLESGEFQIYKQDHSAVVALQIEKIN
NPDKIDSLINQRSFLVSGLGGEHTAFNQLPDGKAEYHGKAFSSDDAGGKLTYTI
DFAAKQGHGKIEHLKTPEQNVELAAAELKADEKSHAVILGDTRYGSEEKGTYH
LALFGDRAQEIAGSATVKIGEKVHEIGIAGKQ

SEC. ID. NRO.: 3.
VAADIGTGLADALTAPLDHKDKGLKSLTLEDSIPQNGTLTLSAQGAEKTFKAGD
KDNSLNTGKLKNDKISRFDFVQKIEVDGQTITLASGEFQIYKQNHSAVVALQIEK

INNPDKTDSLINQRSFLVSGLGGEHTAFNQLPGGKAEYHGKAFSSDDPNGRLHY SIDFTKKQGYGRIEHLKTLEQNVELAAAELKADEKSHAVILGDTRYGSEEKGTY HLALFGDRAQEIAGSATVKIGEKVHEIGIAGKQ.

El valor de a es de por lo menos 85, por ejemplo, 86; 87; 88; 89; 90; 91; 92; 93; 94; 95; 96; 97; 98; 99; 99,5; o más. El valor de b es de por lo menos 85, por ejemplo, 86; 87; 88; 89; 90; 91; 92; 93; 94; 95; 96; 97; 98; 99; 99,5; o más. El valor de c es de por lo menos 85, por ejemplo, 86; 87; 88; 89; 90; 91; 92; 93; 94; 95; 96; 97; 98; 99; 99,5, o más. Los valores de a; b y c no están intrínsecamente relacionados entre sí.

El valor de x es por lo menos 7, por ejemplo, 8; 9; 10; 11; 12; 13; 14; 15; 16; 17; 18; 19; 20; 21; 22; 23; 24; 25; 26; 27; 28; 29; 30; 35; 40; 45; 50; 60; 70; 80; 90; 100; 120; 140; 160; 180; 200; 225; 250. El valor de y es por lo menos 7, por ejemplo, 8; 9; 10; 11; 12; 13; 14; 15; 16; 17; 18; 19; 20; 21; 22; 23; 24; 25; 26; 27; 28; 29; 30; 35; 40; 45; 50; 60; 70; 80; 90; 100; 120; 140; 160; 180; 200; 225; 250. El valor de z es por lo menos 7, por ejemplo, 8; 9; 10; 11; 12; 13; 14; 15; 16; 17; 18; 19; 20; 21; 22; 23; 24; 25; 26; 27; 28; 29; 30; 35; 40; 45; 50; 60; 70; 80; 90; 100; 120; 140; 160; 180; 200; 225; 250. Los valores de x; y y z no están intrínsecamente relacionados entre sí.

En algunas realizaciones, las composiciones inmunógenas que se revelan en la presente solicitud incluirán proteínas fHBP lipidadas, por ejemplo, en una cisteína N–terminal. En otras realizaciones, estas proteínas no serán lipidadas.

Una composición inmunógena útil como se revela en la presente solicitud incluye proteínas purificadas y comprende una mezcla de: (i) un primer polipéptido que tiene la secuencia de aminoácidos de SEC. ID. NRO.: 4; (ii) un segundo polipéptido que tiene la secuencia de aminoácidos de SEC. ID. NRO.: 5; y (iii) un tercer polipéptido que tiene la secuencia de aminoácidos de SEC. ID. NRO.: 6. Ver la referencia de Giuliani *et al.* (2006): *Proc. Natl. Acad. Sci. U. S. A.* 103 (29): 10834–9 y el documento WO 2004/032958. Una composición inmunógena útil

como se revela en la presente solicitud incluye proteínas purificadas y comprende una mezcla de: (i) un primer polipéptido que tiene por lo menos un % a de identidad de secuencia con respecto a la secuencia de aminoácidos de SEC. ID. NRO.: 4; (ii) un segundo polipéptido que tiene por lo menos un % b de identidad de secuencia con respecto a la secuencia de aminoácidos de SEC. ID. NRO.: 5; y (iii) un tercer polipéptido que tiene por lo menos un % a de identidad de secuencia con respecto a la secuencia de aminoácidos de SEC. ID. NRO.: 6.

SEC. ID. NRO.: 4.

MASPDVKSADTLSKPAAPVVSEKETEAKEDAPQAGSQGQGAPSAQGGQDMAA
VSEENTGNGGAAATDKPKNEDEGAQNDMPQNAADTDSLTPNHTPASNMPAGN
MENQAPDAGESEQPANQPDMANTADGMQGDDPSAGGENAGNTAAQGTNQAE
NNQTAGSQNPASSTNPSATNSGGDFGRTNVGNSVVIDGPSQNITLTHCKGDSCS
GNNFLDEEVQLKSEFEKLSDADKISNYKKDGKNDGKNDKFVGLVADSVQMKGI
NQYIIFYKPKPTSFARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSG
NIFAPEGNYRYLTYGAEKLPGGSYALRVQGEPSKGEMLAGTAVYNGEVLHFHT
ENGRPSPSRGRFAAKVDFGSKSVDGIIDSGDGLHMGTQKFKAAIDGNGFKGTWT
ENGGGDVSGKFYGPAGEEVAGKYSYRPTDAEKGGFGVFAGKKEQDGSGGGGA
TYKVDEYHANARFAIDHFNTSTNVGGFYGLTGSVEFDQAKRDGKIDITIPVANL
QSGSQHFTDHLKSADIFDAAQYPDIRFVSTKFNFNGKKLVSVDGNLTMHGKTAP
VKLKAEKFNCYQSPMAKTEVCGGDFSTTIDRTKWGVDYLVNVGMTKSVRIDIQ
IEAAKQ

SEC. ID. NRO.: 5.

MVSAVIGSAAVGAKSAVDRRTTGAQTDDNVMALRIETTARSYLRQNNQTKGY
TPQISVVGYNRHLLLLGQVATEGEKQFVGQIARSEQAAEGVYNYITVASLPRTA
GDIAGDTWNTSKVRATLLGISPATQARVKIVTYGNVTYVMGILTPEEQAQITQK
VSTTVGVQKVITLYQNYVQRGSGGGGVAADIGAGLADALTAPLDHKDKGLQSL
TLDQSVRKNEKLKLAAQGAEKTYGNGDSLNTGKLKNDKVSRFDFIRQIEVDGQ
LITLESGEFQVYKQSHSALTAFQTEQIQDSEHSGKMVAKRQFRIGDIAGEHTSFD
KLPEGGRATYRGTAFGSDDAGGKLTYTIDFAAKQGNGKIEHLKSPELNVDLAA
ADIKPDGKRHAVISGSVLYNQAEKGSYSLGIFGGKAQEVAGSAEVKTVNGIRHI
GLAAKQ

SEC. ID. NRO.: 6.
ATNDDDVKKAATVAIAAAYNNGQEINGFKAGETIYDIDEDGTITKKDATAADV
EADDFKGLGLKKVVTNLTKTVNENKQNVDAKVKAAESEIEKLTTKLADTDAAL
ADTDAALDATTNALNKLGENITTFAEETKTNIVKIDEKLEAVADTVDKHAEAFN
DIADSLDETNTKADEAVKTANEAKQTAEETKQNVDAKVKAAETAAGKAEAAA
GTANTAADKAEAVAAKVTDIKADIATNKDNIAKKANSADVYTREESDSKFVRI
DGLNATTEKLDTRLASAEKSIADHDTRLNGLDKTVSDLRKETRQGLAEQAALS
GLFQPYNVG.

Antígenos de vesículas bacterianas.

Las composiciones inmunógenas que se revelan en la presente solicitud pueden comprender vesículas de membranas externas. Dichas vesículas de membranas externas pueden obtenerse a partir de una amplia gama de bacterias patógenas y utilizarse como componentes antigénicos de las composiciones inmunógenas que se revelan en esta solicitud. Las vesículas para el uso como componentes antigénicos de dichas composiciones inmunógenas incluyen cualquier vesícula proteoliposómica obtenida mediante la interrupción de una membrana externa bacteriana, para formar, a partir de allí, vesículas que incluyen componentes proteicos de la membrana externa. En consecuencia, el término abarca OMV (a veces, denominados "ampollas"), microvesículas (MV, ver, por ejemplo, el documento WO 02/09643) y 'OMV naturales' ('NOMV', ver, por ejemplo, la referencia de Katial *et al.* (2002): *Infect. Immun.* 70: 702–707). Las composiciones inmunógenas que se revelan en esta solicitud que comprenden vesículas de una o más bacterias patógenas pueden usarse en el tratamiento o la prevención de la infección por dichas bacterias patógenas y enfermedades y trastornos relacionados.

Las MV y NOMV son vesículas de membranas naturales que se forman de modo espontáneo durante el crecimiento bacteriano, y son liberadas en el medio de cultivo. Las MV pueden obtenerse mediante el cultivo de bacterias tales como

Neisseria en medio de caldo de cultivo, la separación de las células enteras de las MV más pequeñas en el medio de caldo de cultivo (por ejemplo, por medio de la filtración o la centrifugación a baja velocidad, a fin de miniesferizar solo las células y no las vesículas más pequeñas) y a continuación, la recolección de las MV del medio con reducción de las células (por ejemplo, mediante la filtración, la precipitación diferencial o la agregación de MV, la centrifugación a alta velocidad a fin de miniesferizar las MV). Las cepas para el uso en la producción de MV, en general, pueden seleccionarse sobre la base de la cantidad de MV producida en el cultivo (ver, por ejemplo, la Patente de los Estados Unidos Nro. 6.180.111 y el documento WO 01/34642 que describen *Neisseria* con alta producción de MV).

Las OMV se preparan de manera artificial a partir de bacterias, y pueden prepararse usando tratamiento de detergente (por ejemplo, con desoxicolato), o por medios no detergentes (ver, por ejemplo, el documento WO 04/019977). Los métodos para la obtención de preparaciones de OMV adecuadas son conocidos en el arte. Las técnicas para la formación de OMV incluyen el tratamiento de bacterias con un detergente salino de ácido biliar (por ejemplo, se prefieren sales de ácido litocólico, ácido quenodesoxicólico, ácido ursodesoxicólico, ácido desoxicólico, ácido cólico, ácido ursocólico, etc., con desoxicolato sódico (documento EP 0011243 y referencia de Fredriksen *et al.* (1991): *NIPH Ann.* 14 (2): 67–80) para el tratamiento de *Neisseria*) a un pH suficientemente alto para no precipitar el detergente (ver, por ejemplo, el documento WO 01/91788). Otras técnicas pueden efectuarse esencialmente en ausencia de detergente (ver, por ejemplo, el documento WO 04/019977) usando técnicas tales como sonicación, homogenización, microfluidización, cavitación, choque osmótico, molienda, prensa francesa, combinación, etc. Los métodos que no usan detergente, o que emplean bajas cantidades de detergente, pueden retener antígenos útiles tales como NspA en OMV de *Neisseria*. Por lo tanto, un método puede emplear un regulador de

extracción de OMV con aproximadamente 0,5% de desoxicolato o cantidad inferior, por ejemplo, aproximadamente 0,2%, aproximadamente 0,1%, <0,05% o cero.

Un proceso útil para la preparación de OMV se describe en el documento WO 05/004908 y supone la ultrafiltración sobre OMV en bruto, en lugar de la centrifugación a alta velocidad. El proceso puede involucrar una etapa de ultracentrifugación luego de la etapa de ultrafiltración.

Las vesículas pueden prepararse a partir de cualquier cepa patógena tal como *Neisseria minigtidis* para el uso con la invención. Las vesículas de *Neisserial meningitidis* serogrupo B pueden ser de cualquier serotipo (por ejemplo, 1, 2a, 2b, 4, 14, 15, 16, etc.), cualquier serosubtipo y cualquier immunotipo (por ejemplo, L1; L2; L3; L3,3,7; L10; etc.). Los meningococos pueden ser de cualquier linaje adecuado, por ejemplo, linajes hiperinvasivos e hipervirulentos, tales como cualquiera de los siguientes siete linajes hipervirulentos: subgrupo I; subgrupo III; subgrupo IV 1; complejo ET 5; complejo ET 37; racimo A4; linaje 3. Estos linajes se han definido por medio de la electroforesis enzimática multilocus (MLEE, por sus siglas en inglés), si bien se ha utilizado también la tipificación de secuencia multilocus (MLST, por sus siglas en inglés) a fin de clasificar miningococos, por ejemplo, el complejo ET 37 es el complejo ST 11 por MLST; el complejo ET 5 es ST–32 (ET–5); el linaje 3 es ST 41/44, etc. Las vesículas pueden prepararse a partir de cepas que tienen uno de los siguientes subtipos: P1.2; P1.2,5; P1.4; P1.5; P1.5,2; P1.5,c; P1.5c,10; P1.7,16; P1.7,16b; P1.7h,4; P1.9; P1.15; P1.9,15; P1.12,13; P1.13; P1.14; P1.21,16; P1.22,14.

Las vesículas incluidas en las composiciones inmunógenas que se revelan en la presente solicitud pueden prepararse a partir de cepas patógenas naturales tales como cepas de *N. meningitides* o de cepas mutantes. A modo de ejemplo, el

documento WO 98/56901 revela preparaciones de vesículas obtenidas a partir de *N. meningitidis* con un gen *fur* modificado. El documento WO 02/09746 describe que la expresión de *nspA* debe ser regulada en forma ascendente con el noqueo (*knockout*: una mutante individual donde se ha reemplazado un solo gen funcional por una forma no funcional del gen) de *porA* y *cps* concomitante. Otras mutantes de noqueo de *N. meningitidis* para la producción de OMV se revelan en los documentos WO 02/0974, WO 02/062378 y WO 04/014417. El documento WO 06/081259 revela vesículas en las cuales *fHBP* está regulado en forma ascendente. Claassen *et al.* (1996) 14 (10): 1001–8 revelan la construcción de vesículas a partir de cepas modificadas de manera de expresar seis diferentes subtipos *PorA*. Pueden usarse además mutantes de *Neisseria* con bajos niveles de endotoxinas, logradas mediante el noqueo de enzimas involucradas en la biosíntesis de LPS (ver, por ejemplo, el documento WO 99/10497 y la referencia de Steeghs *et al.* (2001) i20: 6937–6945). Estas u otras mutantes pueden ser utilizadas con la invención.

Por lo tanto, las cepas del serogrupo B de *N. meningitidis* incluidas en las composiciones inmunógenas reveladas en esta invención, en algunas realizaciones, pueden expresar más de un subtipo *PorA*.. Se han construido previamente cepas *PorA* seis valentes y nueve valentes. La cepa puede expresar 2; 3; 4; 5; 6; 7; 8 ó 9 subtipos *PorA*: P1.7,16; P1.5–1,2–2; P1.19,15–1; P1.5–2,10; P1.12 1,13; P1.7–2,4; P1.22,14; P1.7–1,1 y/o P1.18–1,3,6. En otras realizaciones, una cepa puede haber sido regulada en forma descendente para la expresión de *PorA*, por ejemplo, donde la cantidad de *PorA* ha sido reducida por lo menos 20% (por ejemplo, >30%, >40%, >50%, >60%, >70%, >80%, >90%, >95%, etc.), o aun puede haber sido noqueada, en relación con los niveles naturales (por ejemplo, en relación con la cepa H44/76, como se describe en el documento WO 03/105890).

En algunas realizaciones, las cepas de serogrupo B de *N. meningitidis* pueden sobreexpresar (en relación con la correspondiente cepa natural) ciertas proteínas. Por ejemplo, las cepas pueden sobreexpresar NspA, proteína 287 (WO 01/52885 –también denominada NMB2132 y GNA2132), una o más fHBP (WO 06/081259 y Pub. de Patente de los Estados Unidos Nro. 2008/0248065 –también denominada proteína 741, NMB1870 y GNA1870), TbpA y/o TbpB (WO 00/25811), Cu,Zn–superóxido dismutasa (WO 00/25811), etc.

En algunas realizaciones, las cepas de serogrupo B de *N. meningitidis* pueden incluir una o más de las mutaciones de noqueo o sobreexpresión. Los genes preferidos para la regulación descendente o el noqueo incluyen: (a) Cps, CtrA, CtrB, CtrC, CtrD, FrpB, GalE, HtrB/MsbB, LbpA, LbpB, LpxK, Opa, Opc, PilC, PorB, SiaA, SiaB, SiaC, SiaD, TbpA, y/o TbpB (WO 01/09350); (b) CtrA, CtrB, CtrC, CtrD, FrpB, GalE, HtrB/MsbB, LbpA, LbpB, LpxK, Opa, Opc, PhoP, PilC, PmrE, PmrF, SiaA, SiaB, SiaC, SiaD, TbpA, y/o TbpB (WO 02/09746); (c) ExbB, ExbD, rmpM, CtrA, CtrB, CtrD, GalE, LbpA, LpbB, Opa, Opc, PilC, PorB, SiaA, SiaB, SiaC, SiaD, TbpA, y/o TbpB (WO 02/062378); y (d) CtrA, CtrB, CtrD, FrpB, OpA, OpC, PilC, PorB, SiaD, SynA, SynB, y/o SynC (WO04/014417).

Cuando se usa una cepa mutante, en algunas realizaciones, esta puede tener una o más de las siguientes características, o todas ellas: (i) LgtB y/o GalE noqueado o regulado en forma descendente, a fin de truncar el LOS meningocócico; (ii) TbpA regulado en forma ascendente; (iii) Hsf regulado en forma ascendente; (iv) Omp85 regulado en forma ascendente; (v) LbpA regulado en forma ascendente; (vi) NspA regulado en forma ascendente; (vii) PorA noqueado; (viii) FrpB regulado en forma descendente o noqueado; (ix) Opa regulado en forma descendente o noqueado; (x) Opc regulado en forma descendente o noqueado; (xii) complejo de genes cps deleteado. Un LOS truncado puede ser aquel que no incluye un epítopo de sialil–lacto–N–

neotetraosa, por ejemplo, puede ser un LOS deficiente en galactosa. El LOS puede no tener cadena α.

Si se presenta LOS en una vesícula, entonces es posible tratar la vesícula de manera de unir su LOS y componentes proteicos (conjugación "intraampolla" (WO 04/014417)).

Las composiciones inmunógenas que se revelan en la presente solicitud pueden incluir mezclas de vesículas de diferentes cepas. A modo de ejemplo, el documento WO 03/105890 revela vacunas que comprenden composiciones de vesículas meningocócicas multivalentes, que comprenden una primera vesícula derivada de una cepa meningocócica con un serosubtipo predominante en un país de uso, y una segunda vesícula derivada de una cepa que no necesariamente debe tener un serosubtipo predominante en un país de uso. El documento WO 06/024946 revela combinaciones útiles de diferentes vesículas. Una combinación de vesículas de cepas de cada uno de los inmunotipos L2 y L3 puede usare en algunas realizaciones.

Los antígenos a base de vesículas pueden prepararse a partir de serogrupos de *N. meningitides* diferentes del serogrupo B (por ejemplo, el documento WO 01/91788 revela un proceso para el serogrupo A). Las composiciones inmunógenas reveladas en la presente solicitud, en consecuencia, pueden incluir vesículas preparadas con serogrupos diferentes de B (por ejemplo, A, C, W135 y/o Y) y a partir de patógenos bacterianos diferentes de *Neisseria*.

Antígenos virales.

Los antígenos virales adecuados para el uso en las composiciones inmunógenas que se proveen en la presente solicitud incluyen, sin limitación, virus inactivados (o muertos), virus atenuados, formulaciones de virus divididas, formulaciones de subunidades purificadas, proteínas virales que pueden ser aisladas, purificadas o derivadas de un virus, y partículas de tipo viral (VLP, por

sus siglas en inglés). En ciertas realizaciones, los antígenos virales derivan de virus propagados en cultivo celular u otro sustrato. En otras realizaciones, los antígenos virales se expresan en forma recombinada. En ciertas realizaciones, los antígenos virales incluyen, preferentemente, epítopos expuestos sobre la superficie del virus durante por lo menos una etapa de su ciclo de vida. Los antígenos virales, preferentemente, son conservados a través de múltiples serotipos o aislados. Los antígenos virales adecuados para el uso en las composiciones inmunógenas que se proveen en esta solicitud incluyen, sin limitación, antígenos derivados de uno o más de los virus expuestos a continuación, al igual que los ejemplos de antígenos específicos identificados debajo.

Orthomyxovirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de un ortomixovirus, tal como gripe A, B y C. En ciertas realizaciones, los antígenos de ortomixovirus se seleccionan de una o más de las proteínas virales, que incluyen hemaglutinina (HA), neuraminidasa (NA), nucleoproteína (NP), proteína de matriz (M1), proteína de membrana (M2), uno o más de los componentes de transcriptasa (PB1, PB2 y PA). En ciertas realizaciones, el antígeno viral incluye HA y NA. En ciertas realizaciones, los antígenos de la gripe derivan de cepas de gripe interpandémica (anual), mientras que en otras realizaciones, los antígenos de la gripe derivan de cepas con el potencial para causar un brote pandémico (es decir, cepas de la gripe con nueva hemaglutinina, en comparación con la hemaglutinina en cepas actualmente circulantes, o cepas de la gripe que son patógenas en sujetos aviarios y tienen el potencial de ser transmitidas horizontalmente en la población humana, o cepas de la gripe que son patógenas en humanos).

Virus *Paramyxoviridae*. Los antígenos virales incluyen, sin limitación, aquellos derivados de virus *Paramyxoviridae*, tales como neumovirus (RSV), paramixovirus (PIV), metaneumovirus y morbillivirus (sarampión).

Pneumovirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de un neumovirus, tal como el virus sincitial respiratorio (RSV), virus sincitial respiratorio bovino, virus de neumonía del ratón y virus de rinotraqueítis del pavo. Preferentemente, el neumovirus es RSV. En ciertas realizaciones, los antígenos de neumovirus se seleccionan de una o más de las siguientes proteínas, que incluyen fusión de proteínas de superficie (F), glicoproteína (G) y proteína fóbica hidrófoba pequeña (SH), proteínas de matriz M y M2, proteínas nucleocápsidas N, P y L y proteínas no estructurales NS1 y NS2. En otras realizaciones, los antígenos de neumovirus incluyen F, G y M. En ciertas realizaciones, los antígenos de neumovirus se formulan también en virus quiméricos, o derivan de ellos, tales como, solo a modo de ejemplo, virus quiméricos RSV/PIV que comprenden componentes tanto de RSV como de PIV.

Paramyxovirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de un paramixovirus, tal como los virus de paragripe tipos 1–4 (PIV), paperas, virus Sendai, virus simio 5, virus paragripe bovino, nipahvirus, Henipavirus y virus de la enfermedad de Newcastle. En ciertas realizaciones, el paramixovirus es PIV o paperas. En ciertas realizaciones, los antígenos de paramixovirus se seleccionan de una o más de las siguientes proteínas: hemaglutinina–neuraminidasa (HN), proteínas de fusión F1 y F2, nucleoproteína (NP), fosfoproteína (P), proteína grande (L) y proteína de matriz (M). En otras realizaciones, las proteínas de paramixovirus incluyen HN, F1 y F2. En ciertas realizaciones, los antígenos de paramixovirus también se formulan en virus quiméricos, o derivan de ellos, tales como, solo a modo de ejemplo, virus quiméricos RSV/PIV que comprenden componentes tanto de RSV como de PIV.

Las vacunas de paperas comerciales incluyen virus de paperas atenuados, ya sea en forma monovalente, ya sea en combinación con vacunas de sarampión y rubéola (MMR, por sus siglas en inglés). En otras realizaciones, el paramixovirus es Nipahvirus o Henipavirus, y los antígenos se seleccionan de una o más de las siguientes proteínas: proteína de fusión (F), glicoproteína (G), proteína de matriz (M), proteína nucleocápsida (N), proteína grande (L) y fosfoproteína (P).

Poxviridae. Los antígenos virales incluyen, sin limitación, aquellos derivados de *Orthopoxvirus* tales como *Variola vera*, que incluyen, sin limitación, *Variola major* y *Variola minor*.

Metapneumovirus. Los antígenos virales incluyen, sin limitación, metaneumovirus, tales como metaneumovirus humano (hMPV) y metaneumovirus aviar (aMPV). En ciertas realizaciones, los antígenos de metaneumovirus se seleccionan de una o más de las siguientes proteínas, que incluyen fusión de proteínas de superficie (F), glicoproteína (G) y proteína hidrófoba pequeña (SH), proteínas de matriz M y M2, proteínas nucleocápsidas N, P y L. En otras realizaciones, los antígenos de metaneumovirus incluyen F, G y M. En ciertas realizaciones, los antígenos de metaneumovirus también se formulan en virus quiméricos, o derivan de ellos.

Morbillivirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de un morbilivirus, tal como el sarampión. En ciertas realizaciones, los antígenos de morbilivirus se seleccionan de una o más de las siguientes proteínas: hemaglutinina (H), glicoproteína (G), factor de fusión (F), proteína grande (L), nucleoproteína (NP), polimerasa fosfoproteína (P) y matrix (M). Las vacunas del sarampión comerciales incluyen virus del sarampión atenuados vivos, habitualmente, en combinación con paperas y rubéola (MMR).

Picornavirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de picornavirus, tales como enterovirus, rinovirus, heparnavirus,

cardiovirus y aftovirus. En ciertas realizaciones, los antígenos derivan de enterovirus, mientras que en otras realizaciones el enterovirus es poliovirus. En aun otras realizaciones, los antígenos derivan de rinovirus. En ciertas realizaciones, los antígenos se formulan en partículas de tipo viral (VLP).

Enterovirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de un enterovirus, por ejemplo, los tipos de poliovirus 1; 2 ó 3, virus Coxsackie A tipos 1 a 22 y 24; virus Coxsackie B tipos 1 a 6, virus ecovirus (ECHO)) tipos 1 a 9, 11 a 27 y 29 a 34 y enterovirus 68 a 71. En ciertas realizaciones, los antígenos derivan de enterovirus, mientras que en otras realizaciones, el enterovirus es poliovirus. En ciertas realizaciones, los antígenos de enterovirus se seleccionan de una o más de las siguientes proteínas cápsidas: VP0, VP1, VP2, VP3 y VP4. Las vacunas de polio comerciales incluyen vacuna de polio inactivada (IPV, por sus siglas en inglés) y vacuna de poliovirus oral (OPV, por sus siglas en inglés). En ciertas realizaciones, los antígenos se formulan en partículas de tipo viral.

Bunyavirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de un *Orthobunyavirus*, tal como el virus de encefalitis de California, un *Flebovirus*, tal como el virus de fiebre del Valle de Rift, o un *Nairovirus*, tal como el virus de fiebre hemorrágica de Crimean–Congo.

Rhinovirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de rinovirus. En ciertas realizaciones, los antígenos de rinovirus se seleccionan de una o más de las siguientes proteínas cápsidas: VP0, VP1, VP2, VP2 y VP4. En ciertas realizaciones, los antígenos se formulan en partículas de tipo viral (VLP).

Heparnavirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de un heparnavirus, tales como, solo a modo de ejemplo, el virus de la

hepatitis A (HAV). Las vacunas de HAV comerciales incluyen vacuna de HAV inactivada.

Togavirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de un togavirus, tal como un rubivirus, un alfavirus, o un arterivirus. En ciertas realizaciones, los antígenos derivan de rubivirus, tal como, solo a modo de ejemplo, el virus de la rubéola. En ciertas realizaciones, los antígenos de togavirus se seleccionan de E1, E2, E3, C, NSP–1, NSPO–2, NSP–3 o NSP–4. En ciertas realizaciones, los antígenos de togavirus se seleccionan de E1, E2 o E3. Las vacunas de rubéola comerciales incluyen un virus adaptado al frío vivo, habitualmente, en combinación con vacunas de paperas y sarampión (MMR).

Flavivirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de un flavivirus, tal como el virus de encefalitis transportado por ácaros (TBE, por sus siglas en inglés), virus del dengue (tipos 1; 2; 3; ó 4), virus de la fiebre amarilla, virus de encefalitis japonés, virus del bosque de Kyasanur, virus de encefalitis del Nilo occidental, virus de encefalitis de St. Louis, virus de encefalitis de la primavera–verano ruso, virus de encefalitis de Powassan. En ciertas realizaciones, los antígenos de flavivirus se seleccionan de PrM, M, C, E, NS–1, NS–2a, NS2b, NS3, NS4a, NS4b y NS5. En ciertas realizaciones, los antígenos de flavivirus se seleccionan de PrM, M y E. Las vacunas de TBE comerciales incluyen vacunas de virus inactivados. En ciertas realizaciones, los antígenos se formulan en partículas de tipo viral (VLP).

Pestivirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de un pestivirus, tal como el virus de la diarrea viral bovina (BVDV), el virus de la fiebre porcina clásica (CSFV) o el virus de la enfermedad borde (BDV).

Hepadnavirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de un hepadnavirus, tal como el virus de la hepatitis B. En ciertas realizaciones, los antígenos de hepadnavirus se seleccionan de antígenos de

superficie (L, M y S), antígenos de núcleo (HBc, HBe). Las vacunas de HBV comerciales incluyen vacunas subunitarias que comprenden la proteína S de antígeno de superficie.

Virus de la hepatitis C. Los antígenos virales incluyen, sin limitación, aquellos derivados de un virus de la hepatitis C (HCV). En ciertas realizaciones, los antígenos de HCV se seleccionan de uno o más de E1, E2, E1/E2, NS345 poliproteína, NS 345–poliproteína de núcleo, núcleo, y/o péptidos de las regiones no estructurales. En ciertas realizaciones, los antígenos de virus de la hepatitis C comprenden uno o más de los siguientes: HCV proteínas E1 o E2, complejos heterodiméricos E1/E2, proteínas de núcleo y proteínas no estructurales, o fragmentos de estos antígenos, donde las proteínas no estructurales pueden estar opcionalmente modificadas para eliminar la actividad enzimática, pero para retener la inmunogenicidad. En ciertas realizaciones, los antígenos se formulan en partículas de tipo viral (VLP).

Rhabdovirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de un rabdovirus, tal como un *Lissavirus* (virus de la rabia) y vesiculovirus (VSV). Los antígenos de rabdovirus pueden seleccionarse de glicoproteína (G), nucleoproteína (N), proteína grande (L), proteínas no estructurales (NS). Las vacunas del virus de la rabia comerciales comprenden virus muertos cultivados en células diploides humanas o células pulmonares fetales del macaco de la India.

Caliciviridae. Los antígenos virales incluyen, sin limitación, aquellos derivados de *Calciviridae,* tales como el virus de Norwalk y virus de tipo Norwalk, tales como el virus de Hawaii Virus y el virus de Snow Mountain. En ciertas realizaciones, los antígenos se formulan en partículas de tipo viral (VLP).

Coronavirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de un coronavirus, SARS, coronavirus respiratorio humano, bronquitis

infecciosa aviar (IBV), virus de hepatitis del ratón (MHV) y virus de gastroenteritis transmisible porcino (TGEV). En ciertas realizaciones, los antígenos de coronavirus se seleccionan de espiga (S), cubierta (E), matriz (M), nucleocápsido (N) y hemaglutinina–esterasa glicoproteína (HE). En ciertas realizaciones, el antígeno de coronavirus deriva de un virus SARS. En ciertas realizaciones, el coronavirus deriva de un antígeno viral SARS descripto en el documento WO 04/92360.

Retrovirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de un retrovirus, tal como un oncovirus, un lentivirus o un espumavirus. En ciertas realizaciones, los antígenos de oncovirus derivan de HTLV–1, HTLV–2 o HTLV–5. En ciertas realizaciones, los antígenos de lentivirus derivan de HIV–1 o HIV–2. En ciertas realizaciones, los antígenos derivan de subtipos HIV–1 (o revestimientos), que incluyen, sin limitación, subtipos HIV–1 (o revestimientos) A, B, C, D, F, G, H, J. K, O. En otras realizaciones, los antígenos derivan de formas recombinadas circulantes de HIV–1 (CRF), que incluyen, sin limitación, A/B, A/E, A/G, A/G/I, etc. En ciertas realizaciones, los antígenos de retrovirus se seleccionan de gag, pol, env, tax, tat, rex, rev, nef, vif, vpu, y vpr. En ciertas realizaciones, los antígenos de HIV se seleccionan de gag (p24gag y p55gag), env (gp160 y gp41), pol, tat, nef, rev vpu, miniproteínas (preferentemente, p55 gag y gp140v deleción). En ciertas realizaciones, los antígenos de HIV derivan de una o más de las siguientes cepas: HIV_{IIIb}, HIV_{SF2}, HIV_{LAV}, HIV_{LAI}, HIV_{MN}, $HIV\text{–}1_{CM235}$, $HIV\text{–}1_{US4}$, $HIV\text{–}1_{SF162}$, $HIV\text{–}1_{TV1}$, $HIV\text{–}1_{MJ4}$. En ciertas realizaciones, los antígenos derivan de retrovirus humanos endógenos, que incluyen, sin limitación, HERV–K ("antiguo" HERV–K y "nuevo" HERV–K).

Reovirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de un reovirus, tales como un ortorreovirus, un rotavirus, un Orbivirus, o un coltivirus. En ciertas realizaciones, los antígenos de reovirus se seleccionan de

proteínas estructurales λ1, λ2, λ3, μ1, μ2, σ1, σ2, o σ3, o proteínas no estructurales σNS, μNS, o σ1s. En ciertas realizaciones, los antígenos de reovirus derivan de un rotavirus. En ciertas realizaciones, los antígenos de rotavirus se seleccionan de VP1, VP2, VP3, VP4 (o el producto disociado VP5 y VP8), NSP 1, VP6, NSP3, NSP2, VP7, NSP4, o NSP5. En ciertas realizaciones, los antígenos de rotavirus incluyen VP4 (o el producto disociado VP5 y VP8) y VP7.

Parvovirus. Los antígenos virales incluyen, sin limitación, aquellos derivados de un parvovirus, tal como parvovirus B19. En ciertas realizaciones, los antígenos de parvovirus se seleccionan de VP–1, VP–2, VP–3, NS–1 y NS–2. En ciertas realizaciones, el antígeno de parvovirus es proteína cápsida VP1 o VP–2. En ciertas realizaciones, los antígenos se formulan en partículas de tipo viral (VLP).

Virus de hepatitis delta (HDV). Los antígenos virales incluyen, sin limitación, aquellos derivados de HDV, en particular, antígeno δ de HDV.

Virus de hepatitis E (HEV). Los antígenos virales incluyen, sin limitación, aquellos derivados de HEV.

Virus de hepatitis G (HGV). Los antígenos virales incluyen, sin limitación, aquellos derivados de HGV.

Herpesvirus humano. Los antígenos virales incluyen, sin limitación, aquellos derivados de un virus de herpes humano, tal como, solo a modo de ejemplo, virus de herpes simple (HSV), virus de varicela–zoster (VZV), virus de Epstein–Barr (EBV), citomegalovirus (CMV), herpesvirus 6 humano (HHV6), herpesvirus 7 humano (HHV7) y herpesvirus 8 humano (HHV8). En ciertas realizaciones, los antígenos de herpesvirus humanos se seleccionan de proteínas anteriores inmediatas (α), proteínas anteriores (β) y proteínas posteriores (γ). En ciertas realizaciones, los antígenos de HSV derivan de cepas HSV–1 o HSV–2. En ciertas realizaciones, los antígenos de HSV se seleccionan de glicoproteínas

gB, gC, gD y gH, proteína de fusión (gB), o proteínas de escape inmunitario (gC, gE, o gI). En ciertas realizaciones, los antígenos de VZV se seleccionan de núcleo, nucleocápsido, tegumento, o proteínas de cubierta. Una vacuna de VZV atenuada viva puede obtenerse en el mercado. En ciertas realizaciones, los antígenos de EBV se seleccionan de proteínas de antígeno anterior (EA), antígeno cápsido viral (VCA) y glicoproteínas del antígeno de membrana (MA). En ciertas realizaciones, los antígenos de CMV se seleccionan de proteínas cápsidas, glicoproteínas de cubierta (tales como gB y gH) y proteínas de tegumento. En otras realizaciones, los antígenos de CMV pueden seleccionarse de una o más de las siguientes proteínas: pp65, IE1, gB, gD, gH, gL, gM, gN, gO, UL128, UL129, gUL130, UL150, UL131, UL33, UL78, US27, US28, RL5A, RL6, RL10, RL11, RL12, RL13, UL1, UL2, UL4, UL5, UL6, UL7, UL8, UL9, UL10, UL11, UL14, UL15A, UL16, UL17, UL18, UL22A, UL38, UL40, UL41A, UL42, UL116, UL119, UL120, UL121, UL124, UL132, UL147A, UL148, UL142, UL144, UL141, UL140, UL135, UL136, UL138, UL139, UL133, UL135, UL148A, UL148B, UL148C, UL148D, US2, US3, US6, US7, US8, US9, US10, US11, US12, US13, US14, US15, US16, US17, US18, US19, US20, US21, US29, US30 y US34A. Los antígenos de CMV además pueden ser fusiones de una o más proteínas CMV, tales como, solo a modo de ejemplo, pp65/IE1 (Reap *et al.*, *Vaccine* (2007) 25: 7441–7449). En ciertas realizaciones, los antígenos se formulan en partículas de tipo viral (VLP).

Papovaviruses. Los antígenos virales incluyen, sin limitación, aquellos derivados de papovavirus, tales como papilomavirus y poliomavirus. En ciertas realizaciones, los papilomavirus incluyen los serotipos de HPV 1; 2; 4; 5; 6; 8; 11; 13; 16; 18; 31; 33; 35; 39; 41; 42; 47; 51: 57; 58; 63 y 65. En ciertas realizaciones, los antígenos de HPV derivan de lso serotipos 6; 11; 16 ó 18. En ciertas realizaciones, los antígenos de HPV se seleccionan de proteínas cápsidas (L1) y

(L2), o E1 – E7, o sus fusiones. En ciertas realizaciones, los antígenos de HPV se formulan en partículas de tipo viral (VLP). En ciertas realizaciones, los virus de poliomiavirus incluyen virus BK y virus JK. En ciertas realizaciones, los antígenos de poliomavirus se seleccionan de VP1, VP2 o VP3.

Adenovirus. Los antígenos incluyen aquellos derivados de adenovirus. En ciertas realizaciones, los antígenos de adenovirus derivan de adenovirus serotipo 36 (Ad–36). En ciertas realizaciones, el antígeno deriva de una proteína o secuencia de péptido que codifica una proteína de cubierta Ad–36 o uno de sus fragmentos (WO 2007/120362).

Se proveen, adicionalmente, antígenos, composiciones, métodos y microbios utilizados en *Vaccines*, 4$^{ta.}$ Edición (Plotkin and Orenstein ed. 2004); *Medical Microbiology* 4$^{ta.}$ Edición (Murray *et al.* ed. 2002); *Virology*, 3ra. Edición (W.K. Joklik ed. 1988); *Fundamental Virology*, 2da. Edición (B. N. Fields y D. M. Knipe, eds. 1991), que se contemplan en conjunto con las composiciones inmunógenas proporcionadas en la presente solicitud.

Antígenos fúngicos.

Los antígenos fúngicos para el uso en las composiciones inmunógenas que se proveen en la presente solicitud incluyen, sin limitación, aquellos derivados de uno o más de los hongos expuestos a continuación.

Los antígenos fúngicos derivan de dermatofitos, que incluyen: *Epidermophyton floccusum, Microsporum audouini, Microsporum canis, Microsporum distortum, Microsporum equinum, Microsporum gypsum, Microsporum nanum, Trichophyton concentricum, Trichophyton equinum, Trichophyton gallinae, Trichophyton gypseum, Trichophyton megnini, Trichophyton mentagrophytes, Trichophyton quinckeanum, Trichophyton rubrum, Trichophyton schoenleini, Trichophyton tonsurans, Trichophyton verrucosum, T.*

verrucosum var. album, var. discoides, var. ochraceum, *Trichophyton violaceum,* y *Trichophyton faviforme;* y

los patógenos fúngicos derivan de *Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger, Aspergillus nidulans, Aspergillus terreus, Aspergillus sydowi, Aspergillus flavatus, Aspergillus glaucus, Blastoschizomyces capitatus, Candida albicans, Candida enolase, Candida tropicalis, Candida glabrata, Candida krusei, Candida parapsilosis, Candida stellatoidea, Candida kusei, Candida parakwsei, Candida lusitaniae, Candida pseudotropicalis, Candida guilliermondi, Cladosporium carrionii, Coccidioides immitis, Blastomyces dermatidis, Cryptococcus neoformans, Geotrichum clavatum, Histoplasma capsulatum, Klebsiella pneumoniae, Microsporidia,* género *Encephalitozoon*, *Septata intestinalis* y *Enterocytozoon bieneusi*; los menos comunes son el género *Brachiola*, género *Microsporidium*, género *Nosema*, género *Pleistophora*, género *Trachipleistophora*, género *Vittaforma, Paracoccidioides brasiliensis, Pneumocystis carinii, Pythiumn insidiosum, Pityrosporum ovale, Sacharomyces cerevisae, Saccharomyces boulardii, Saccharomyces pombe, Scedosporium apiosperum, Sporothrix schenckii, Trichosporon beigelii, Toxoplasma gondii, Penicillium marneffei,* género *Malassezia,* género *Fonsecaea*, género *Wangiella*, género *Sporothrix*, género *Basidiobolus*, género *Conidiobolus*, género *Rhizopus*, género *Mucor*, género *Absidia*, género *Mortierella*, género *Cunninghamella,* género *Saksenaea*, género *Alternaria*, género *Curvularia*, género *Helminthosporium*, género *Fusarium*, género *Aspergillus,* género *Penicillium,* género *Monolinia*, género *Rhizoctonia*, género *Paecilomyces*, género *Pithomyces* y género *Cladosporium*.

En ciertas realizaciones, el proceso para la producción de un antígeno fúngico comprende un método donde una fracción solubilizada es extraída y separada de una fracción insoluble que se obtiene de células fúngicas, de las

cuales se ha sustancialmente removido o por lo menos parcialmente removido la pared celular, que se caracteriza porque el proceso comprende las etapas de: la obtención de células fúngicas vivas; la obtención de células fúngicas de las cuales se ha sustancialmente removido o por lo menos parcialmente removido la pared celular; el estallido de las células fúngicas de las cuales se ha sustancialmente removido o por lo menos parcialmente removido la pared celular; la obtención de una fracción insoluble; y la extracción y separación de una fracción solubilizada de la fracción insoluble.

Patógenos/antígenos protozoales.

Los patógenos y antígenos protozoales para el uso en las composiciones inmunógenas proporcionadas en esta solicitud incluyen, sin limitación, aquellos derivados de una o más de los siguientes protozoos: *Entamoeba histolytica*, *Giardia lambli, Cryptosporidium parvum*, *Cyclospora cayatanensis* y *Toxoplasma*.

Patógenos/antígenos de plantas.

Los patógenos y antígenos de plantas para el uso en las composiciones inmunógenas que se proveen en esta solicitud incluyen, sin limitación, aquellos derivados de *Ricinus communis.*

Antígenos de STD.

En ciertas realizaciones, las composiciones inmunógenas proporcionadas en la presente solicitud comprenden uno o más antígenos derivados de una enfermedad de transmisión sexual (STD). En ciertas realizaciones, dichos antígenos proporcionan la profilaxis para una STD tal como clamidia, herpes genital, hepatitis (tal como HCV), verrugas genitales, gonorrea, sífilis o chancro blando. En otras realizaciones, dichos antígenos proveen el tratamiento para STD tales como clamidia, herpes genital, hepatitis (tal como HCV), verrugas genitales, gonorrea, sífilis y chancro blando. Dichos antígenos derivan de una o más STD virales o bacterianas. En ciertas realizaciones, los antígenos de STD virales

derivan de HIV, virus de herpes simple (HSV–1 y HSV–2), virus de papiloma humano (HPV) y hepatitis (HCV). En ciertas realizaciones, los antígenos de STD bacterianos derivan de *Neiserria gonorrhoeae, Chlamydia trachomatis, Treponema pallidum*, *Haemophilus ducreyi*, *E. coli* y *Streptococcus agalactiae.* Ejemplos de antígenos específicos derivan de estos patógenos descriptos anteriormente.

Antígenos respiratorios.

En ciertas realizaciones, las composiciones inmunógenas proporcionadas en la presente solicitud incluyen uno o más antígenos derivados de un patógeno que causa enfermedad respiratoria. Solo a modo de ejemplo, dichos antígenos respiratorios derivan de un virus respiratorio tal como ortomixovirus (gripe), neumovirus (RSV), paramixovirus (PIV), morbilivirus (sarampión), togavirus (rubéola), VZV y coronavirus (SARS). En ciertas realizaciones, los antígenos respiratorios derivan de una bacteria que causa enfermedad respiratoria, tal como, solo a modo de ejemplo, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Bordetella pertussis*, *Mycobacterium tuberculosis*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Bacillus anthracis* y *Moraxella catarrhalis.* Ejemplos de antígenos específicos derivan de estos patógenos descriptos anteriormente.

Antígenos de vacunas pediátricas.

En ciertas realizaciones, las composiciones inmunógenas proporcionadas en la presente solicitud incluyen uno o más antígenos adecuados para el uso en sujetos pediátricos. Los sujetos pediátricos típicamente tienen menos de aproximadamente 3 años de edad, o menos de aproximadamente 2 años de edad, o menos de aproximadamente 1 año de edad. Los antígenos pediátricos se administran múltiples veces durante el curso de 6 meses, 1; 2 ó 3 años. Los antígenos pediátricos derivan de un virus que puede dirigirse a poblaciones

pediátricas, o de un virus a cuya infección es sensible la población pediátrica. Los antígenos virales pediátricos incluyen, sin limitación, antígenos derivados de uno o más de ortomixovirus (gripe), neumovirus (RSV), paramixovirus (PIV y paperas), morbilivirus (sarampión), togavirus (rubéola), enterovirus (polio), HBV, coronavirus (SARS) y virus de varicela–zoster (VZV), virus de Epstein Barr (EBV). Los antígenos bacterianos pediátricos incluyen antígenos derivados de una o más de *Streptococcus pneumoniae*, *Neisseria meningitides*, *Streptococcus pyogenes* (estreptococo Grupo A), *Moraxella catarrhalis*, *Bordetella pertussis*, *Staphylococcus aureus*, *Clostridium tetani* (tétanos), *Cornynabacterium diphtheriae* (difteria), *Haemophilus influenzae B* (Hib), *Pseudomonas aeruginosa*, *Streptococcus agalactiae* (estreptococo Grupo B) y *E. coli*. Ejemplos de antígenos específicos derivados de estos patógenos se describen anteriormente.

Antígenos adecuados para el uso en individuos ancianos o inmunocomprometidos.

En ciertas realizaciones, las composiciones inmunógenas proporcionadas en la presente solicitud incluyen uno o más antígenos adecuados para el uso en individuos ancianos o inmunocomprometidos. Puede ser necesario vacunar a dichos individuos con más frecuencia, con dosis mayores o con formulaciones con coadyuvantes a fin de mejorar su respuesta inmunitaria a los antígenos blanco. Lso antígenos blanco para el uso en individuos ancianos o inmunocomprometidos incluyen antígenos derivados de uno o más de los siguientes patógenos: *Neisseria meningitides, Streptococcus pneumoniae, Streptococcus pyogenes* (estreptococo Grupo A), *Moraxella catarrhalis, Bordetella pertussis, Staphylococcus aureus, Staphylococcus epidermis, Clostridium tetani* (tétano), *Cornyneabacterium diphtheriae* (difteria), *Haemophilus influenzae B (Hib)*, *Pseudomonas aeruginosa, Legionella pneumophila*, *Streptococcus agalactiae* (estreptococo Grupo B), *Enterococcus faecalis, Helicobacter pylori*, *Chlamydia*

pneumoniae, Orthomyxovirus (gripe), *Pneumovirus* (RSV), *Paramyxovirus* (PIV y paperas), *Morbillivirus* (sarampión), *Togavirus* (rubéola), *Enterovirus* (polio), HBV, *Coronavirus* (SARS), virus de varicela–zoster (VZV), virus de Epstein Barr (EBV), Citomegalovirus (CMV). Ejemplos de antígenos específicos derivados de estos patógenos se describen con anterioridad.

Antígenos adecuados para el uso en vacunas para adolescentes.

En ciertas realizaciones, las composiciones inmunógenas proporcionadas en la presente solicitud incluyen uno o más antígenos adecuados para el uso en sujetos adolescentes. Los adolescentes necesitan un refuerzo de un antígeno pediátrico previamente administrado. Los antígenos pediátricos adecuados para el uso en adolescentes se describen anteriormente. Además, los adolescentes son blanco para la recepción de antígenos derivados de un patógeno de STD, a fin de garantizar la inmunidad protectora o terapéutica antes del inicio de la actividad sexual. Los antígenos de STD adecuados para el uso en adolescentes se describen con anterioridad.

Antígenos tumorales.

En ciertas realizaciones, se usa un antígeno tumoral u oncológico en conjunto con las composiciones inmunógenas proporcionadas en la presente solicitud. En ciertas realizaciones, los antígenos tumorales son antígenos tumorales que contienen péptidos, tales como un antígeno tumoral polipeptídico o un antígeno tumoral glicoproteico. En ciertas realizaciones, el antígeno tumoral es un antígeno tumoral que contiene sacárido, tal como un antígeno tumoral glicolípido o un antígeno tumoral ganglíosido. En ciertas realizaciones, el antígeno tumoral es un antígeno tumoral que contiene polinucleótido que expresa un antígeno tumoral que contiene polipéptido, por ejemplo, una construcción de vector de ARN o una construcción de vector de ADN, tal como ADN plásmido.

Los antígenos tumorales apropiados para el uso en conjunto con las

composiciones inmunógenas proporcionadas en la presente solicitud abarcan una amplia variedad de moléculas, tales como: (a) antígenos tumorales que contienen polipéptido, que incluyen polipéptido (que pueden variar, por ejemplo, de 8–20 aminoácidos de longitud, si bien las longitudes fuera de este rango también son comunes), lipopolipéptidos y glicoproteínas; (b) antígenos tumorales que contienen sacárido, que incluyen polisacáridos, mucinas, gangliósidos, glicolípidos y glicoproteínas; y (c) polinucleótidos que expresan polipéptidos antigénicos.

En ciertas realizaciones, los antígenos tumorales son, por ejemplo, (a) moléculas de longitud completa asociadas con células neoplásicas; (b) homólogos y formas modificadas de estas, que incluyen moléculas con porciones deleteadas, agregadas o sustituidas; y (c) fragmentos de estas. En ciertas realizaciones, los antígenos tumorales se proporcionan en forma recombinada. En ciertas realizaciones, los antígenos tumorales incluyen, por ejemplo, antígenos restringidos clase I reconocidos por linfocitos CD8+, o antígenos restringidos clase II reconocidos por linfocitos CD4+.

En ciertas realizaciones, los antígenos tumorales incluyen, sin limitación, (a) antígenos testiculares oncológicos tales como NY–ESO–1, SSX2, SCP1, al igual que los polipéptidos de las familias RAGE, BAGE, GAGE y MAGE, por ejemplo, GAGE–1, GAGE–2, MAGE–1, MAGE–2, MAGE–3, MAGE–4, MAGE–5, MAGE–6 y MAGE–12 (que pueden usarse, por ejemplo, a fin de dirigirse a tumores de melanoma, pulmón, cabeza y cuello, NSCLC, mama, gastrointestinales y de vejiga), (b) antígenos mutados, por ejemplo, p53 (asociado con diversos tumores sólidos, por ejemplo, cáncer colorrectal, pulmonar, de cabeza y cuello), p21/Ras (asociado con, por ejemplo, melanoma, cáncer pancreático y cáncer colorrectal), CDK4 (por ejemplo, asociado con melanoma), MUM1 (asociado con, por ejemplo, melanoma), caspasa–8 (por ejemplo, asociada con cáncer de cabeza y cuello), CIA 0205 (asociado con, por ejemplo, cáncer de

vejiga), HLA–A2–R1701, beta catonina (asociada, por ejemplo, con melanoma), TCR (asociado, por ejemplo, con linfoma no hodgkiniano de célula T), BCR–abl (asociado, por ejemplo, con leucemia mielógena crónica), triosafosfato isomerasa, KIA 0205, CDC–27 y LDLR–FUT; (c) antígenos sobreexpresados, por ejemplo, Galectina 4 (asociada, por ejemplo, con cáncer colorrectal), Galectina 9 (asociada, por ejemplo, con la enfermedad de Hodgkin), proteinasa 3 (asociada, por ejemplo, con leucemia mielógena crónica), WT 1 (asociado, por ejemplo, con diversas leucemias), anhidrasa carbónica (asociada, por ejemplo, con cáncer renal), aldolasa A (asociada, por ejemplo, con cáncer de pulmón), PRAME (asociado, por ejemplo, con melanoma), HER–2/neu (asociado, por ejemplo, con cáncer de mama, colon, pulmón y ovario), alfa–fetoproteina (asociada, por ejemplo, con hepatoma), KSA (asociada, por ejemplo, con cáncer colorrectal), gastrina (asociada, por ejemplo, con cáncer pancreático y gástrico), proteína catalítica telomerasa, MUC–1 (asociado, por ejemplo, con cáncer de mama y ovario), G–250 (asociado, por ejemplo, con carcinoma de célula renal), p53 (asociado, por ejemplo, con cáncer de mama, colon) y antígeno carcinoembriónico (asociado, por ejemplo, con cáncer de mama, pulmón, y tipos de cáncer del tracto gastrointestinal, tales como cáncer colorrectal), (d) antígenos compartidos, por ejemplo, antígenos de diferenciación de melanoma–melanocito tales como MART–1/Melan A, gp100, MC1R, receptor de la hormona estimulante de melanocitos, tirosinasa, proteína relacionada con tirosinasa–1/TRP1 y proteína relacionada con tirosinasa–2/TRP2 (asociadas, por ejemplo, con melanoma), (e) antígenos asociados con la próstata, tales como PAP, PSA, PSMA, PSH–P1, PSM–P1, PSM–P2, asociados, por ejemplo, con cáncer de próstata; (f) idiotipos de inmunoglobulina (asociados con mieloma y linfomas de células B, por ejemplo), y (g) otros antígenos tumorales, tales como antígenos que contienen polipéptido y sacárido que incluyen (i) glicoproteínas tales como sialil Tn y sialil

Le^x (asociadas, por ejemplo, con cáncer de mama y colorrectal), al igual que diversas mucinas; las glicoproteínas se acoplan a una proteína portadora (por ejemplo, MUC–1 se acoplan a KLH); (ii) lipopolipéptidos (por ejemplo, MUC–1 ligado a una porción lípida); (iii) polisacáridos (por ejemplo, hexasacárido sintético Globo H), que pueden acoplarse a proteínas portadoras (por ejemplo, a KLH), (iv) gangliósidos tales como GM2, GM12, GD2, GD3 (asociados, por ejemplo, con cáncer cerebral, pulmonar, melanoma), que también pueden acoplarse a proteínas portadoras (por ejemplo, KLH).

En ciertas realizaciones, los antígenos tumorales incluyen, sin limitación, p15, Hom/Mel–40, H–Ras, E2A–PRL, H4–RET, IGH–IGK, MYL–RAR, antígenos del virus de Epstein Barr, EBNA, antígenos del virus de papiloma humano (HPV), que incluyen E6 y E7, antígenos de virus de hepatitis B y C, antígenos de virus linfotróficos de células T humanas, TSP–180, p185erbB2, p180erbB–3, c–met, mn–23H1, TAG–72–4, CA 19–9, CA 72–4, CAM 17.1, NuMa, K–ras, p16, TAGE, PSCA, CT7, 43–9F, 5T4, 791 Tgp72, beta–HCG, BCA225, BTAA, CA 125, CA 15–3 (CA 27.29\BCAA), CA 195, CA 242, CA–50, CAM43, CD68\KP1, CO–029, FGF–5, Ga733 (EpCAM), HTgp–175, M344, MA–50, MG7–Ag, MOV18, NB/70K, NY–CO–1, RCAS1, SDCCAG16, TA–90 (proteína de unión Mac–2/proteína asociada a ciclofilina C), TAAL6, TAG72, TLP, TPS y similares.

Los antígenos que contienen polinucleótidos utilizados en conjunto con las composiciones inmunógenas que se proveen en esta solicitud incluyen polinucleótidos que codifican antígenos neoplásicos polipeptídicos tales como aquellos citados con anterioridad. En ciertas realizaciones, los antígenos que contienen polinucleótidos incluyen, sin limitación, construcciones de vectores de ADN o ARN, tales como vectores plásmidos (por ejemplo, pCMV), que pueden expresar antígenos neoplásicos polipeptídicos *in vivo*.

En ciertas realizaciones, los antígenos tumorales derivan de componentes

celulares mutados o alterados. Después de la alteración, los componentes celulares ya no efectúan sus funciones regulatorias, y en consecuencia, la célula puede experimentar crecimiento descontrolado. Ejemplos representativos de componentes celulares alterados incluyen, sin limitación, ras, p53, Rb, proteína alterada codificada por el gen del tumor de Wilm, ubiquitina, mucina, proteína codificada por los genes DCC, APC y MCC, al igual que estructuras de receptores o de tipo receptor tales como neu, receptor de hormona tiroidea, receptor de factor de crecimiento derivado de plaqueta (PDGF), receptor de insulina, receptor de factor de crecimiento epidérmico (EGF) y el receptor de factor estimulante de colonias (CSF).

Además, se usan antígenos virales y bacterianos en conjunto con las composiciones inmunógenas proporcionadas en esta solicitud para el tratamiento de cáncer. En ciertas realizaciones, las proteínas portadoras, tales como CRM_{197}, toxoide de tétanos o antígeno de *Salmonella typhimurium,* se usan en conjunto o en conjugación con los compuestos proporcionados en la presente solicitud para el tratamiento de cáncer. Los tratamientos de combinación de antígenos neoplásicos mostrarán mayor eficacia y biodisponibilidad en comparación con los tratamientos existentes.

En ciertas realizaciones, las composiciones inmunógenas que contienen por lo menos un compuesto de la Fórmula (I) comprenden sacáridos capsulares de por lo menos dos de los serogrupos A, C, W135 e Y de *Neisseria meningitides.* En otras realizaciones, dichas vacunas además comprenden un antígeno de uno o más de los siguientes: (a) *N. meningitidis* serogrupo B; (b) *Haemophilus influenzae* tipo B; y (c) *Streptococcus pneumoniae.*

En ciertas realizaciones, las composiciones inmunógenas que contienen por lo menos un compuesto de la Fórmula (I) incluyen los serogrupos C, W135 e Y de *N. meningitides.* En ciertas realizaciones, las composiciones inmunógenas

que contienen por lo menos un compuesto de la Fórmula (I) incluyen los serogrupos A, C, W135 e Y de *N. meningitides*. En ciertas realizaciones, las composiciones inmunógenas que contienen por lo menos un compuesto de la Fórmula (I) incluyen los serogrupos B, C, W135 e Y de *N. meningitides*. En ciertas realizaciones, las composiciones inmunógenas que contienen por lo menos un compuesto de la Fórmula (I) incluyen los serogrupos A, B, C, W135 e Y de *N. meningitides*. En ciertas realizaciones, las composiciones inmunógenas que contienen por lo menos un compuesto de la Fórmula (I) incluyen *H. influenzae* tipo B y los serogrupos C, W135 e Y de *N. meningitides*. En ciertas realizaciones, las composiciones inmunógenas que contienen por lo menos un compuesto de la Fórmula (I) incluyen *H. influenzae* tipo B y los serogrupos A, C, W135 e Y de *N. meningitides*. En ciertas realizaciones, las composiciones inmunógenas que contienen por lo menos un compuesto de la Fórmula (I) *H. influenzae* tipo B y los serogrupos B, C, W135 e Y de *N. meningitides*. En ciertas realizaciones, las composiciones inmunógenas que contienen por lo menos un compuesto de la Fórmula (I) incluyen *H. influenzae* tipo B y los serogrupos A, B, C, W135 e Y de *N. meningitides*. En ciertas realizaciones, las composiciones inmunógenas que contienen por lo menos un compuesto de la Fórmula (I) incluyen *S. pneumoniae* y los serogrupos C, W135 e Y de *N. meningitides*. En ciertas realizaciones, las composiciones inmunógenas que contienen por lo menos un compuesto de la Fórmula (I) incluyen *S. pneumoniae* y los serogrupos A, C, W135 e Y de *N. meningitides*. En ciertas realizaciones, las composiciones inmunógenas que contienen por lo menos un compuesto de la Fórmula (I) incluyen *S. pneumoniae* y los serogrupos B, C, W135 e Y de *N. meningitides*. En ciertas realizaciones, las composiciones inmunógenas que contienen por lo menos un compuesto de la Fórmula (I) incluyen *S. pneumoniae* y los serogrupos A, B, C, W135 e Y de *N. meningitides*. En ciertas realizaciones, las composiciones inmunógenas que

contienen por lo menos un compuesto de la Fórmula (I) incluyen *H. influenzae* tipo B, *S. pneumoniae* y los serogrupos C, W135 e Y de *N. meningitides*. En ciertas realizaciones, las composiciones inmunógenas que contienen por lo menos un compuesto de la Fórmula (I) incluyen *H. influenzae* tipo B, *S. pneumoniae* y los serogrupos A, C, W135 e Y de *N. meningitides*. En ciertas realizaciones, las composiciones inmunógenas que contienen por lo menos un compuesto de la Fórmula (I) incluyen *H. influenzae* tipo B, *S. pneumoniae* y los serogrupos B, C, W135 e Y de *N. meningitides*. En ciertas realizaciones, las composiciones inmunógenas que contienen por lo menos un compuesto de la Fórmula (I) incluyen *H. influenzae* tipo B, *S. pneumoniae* y los serogrupos A, B, C, W135 e Y de *N. meningitidis*.

Equipos.

En la presente solicitud, se proveen además envases o equipos que comprenden uno o más recipientes que contienen un compuesto de las Fórmulas (I)–(XVI), útiles para el tratamiento o la prevención de una enfermedad o un trastorno asociado con los receptores de tipo toll. En otras realizaciones, dichos envases o equipos farmacéuticos incluyen uno o más recipientes que contienen un compuesto de las Fórmulas (I)–(XVI) útiles para el tratamiento o la prevención de una enfermedad o un trastorno asociado con los receptores de tipo toll, y uno o más recipientes que contienen un agente terapéutico adicional, que incluye, sin limitación, aquellos citados con anterioridad. En ciertas realizaciones, dichos envases o equipos farmacéuticos incluyen, en forma opcional, instrucciones para la administración de un compuesto de las Fórmulas (I)–(XVI) como se revelan en esta solicitud. En algunas realizaciones de dichos equipos, el compuesto de las Fórmulas (I)–(XVI) se provee en forma de una composición de vacuna como se describe en la presente solicitud, y opcionalmente, incluye una jeringuilla para la inyección de la composición de vacuna a un sujeto.

Métodos para el tratamiento, la prevención y la administración de vacunas.

Las composiciones inmunógenas que se revelan en la presente solicitud pueden usarse en conjunto con vacunas a fin de mejorar la inmunogenicidad de la vacuna, o cuando la composición inmunógena comprende uno o más antígenos, la composición inmunógena puede usarse como una vacuna. Por lo tanto, en ciertas realizaciones, las composiciones inmunógenas que se revelan en la presente solicitud pueden usarse en un método para la producción o mejoría de una respuesta inmunitaria en un mamífero, que comprende la etapa de la administración de una cantidad eficaz de una composición inmunógena como se revela en la presente solicitud. La respuesta inmunitaria, preferentemente, es protectora, y preferentemente, involucra anticuerpos e inmunidad celular. El método puede producir una respuesta de refuerzo.

En ciertas realizaciones, las composiciones inmunógenas reveladas en la presente solicitud pueden usarse como un medicamento, por ejemplo, para el uso en la producción o mejoría de una respuesta inmunitaria en un mamífero.

En ciertas realizaciones, las composiciones inmunógenas reveladas en la presente solicitud pueden usarse en la elaboración de un medicamento para la producción de una respuesta inmunitaria en un mamífero.

La invención además proporciona un dispositivo de suministro precargado con una composición inmunógena revelada en esta solicitud.

Mediante la producción de una respuesta inmunitaria en el mamífero por medio de estos usos y métodos, la infección del mamífero por patógenos que comprenden el antígeno incluido en la composición inmunógena o administrado en conjunto con la composición inmunógena puede reducirse o aun evitarse. Preferentemente, el mamífero es un ser humano, si bien puede ser, por ejemplo, un cerdo, una vaca, un pollo, gato o perro, ya que los patógenos cubiertos por esta invención pueden representar un problema a través de un amplio rango de

especies. Cuando la vacuna es para uso profiláctico, el ser humano, preferentemente, es un niño (por ejemplo, un lactante o niño menor de 1 año) o un adolescente; cuando la vacuna es para uso terapéutico, preferentemente, el ser humano es un adolescente o un adulto. Una vacuna propuesta para niños además puede administrarse a adultos, por ejemplo, a fin de evaluar la seguridad, la dosificación, inmunogenicidad, etc.

Una forma para controlar la eficacia del tratamiento terapéutico supone el control de la infección del patógeno luego de la administración de las composiciones inmunógenas reveladas en esta invención. Una forma de controlar la eficacia del tratamiento profiláctico supone el control de las respuestas inmunitarias, en forma sistémica (tal como el control del nivel de producción de IgG1 e IgG2) y mucosal (por ejemplo, el control del nivel de producción de IgA) contra los antígenos incluidos o administrados en conjunto con las composiciones inmunógenas descriptas en la presente solicitud, luego de la administración de la composición inmunógena (y el antígeno, si se administran en forma separada). Habitualmente, las respuestas de anticuerpos séricos específicas de antígeno se determinan luego de la inmunización, si bien, antes de la estimulación, mientras que las respuestas de anticuerpos mucosales específicas de antígenos se determinan luego de la inmunización y de la estimulación.

Otra manera de evaluar la inmunogenicidad de las composiciones inmunógenas reveladas en la presente solicitud, donde el antígeno es una proteína, es la expresión de las proteínas en forma biotecnológica para la detección sistemática del suero del paciente o de secreciones mucosas del paciente, mediante inmunoblot o microseries. Una reacción positiva entre la proteína y la muestra del paciente indica que el paciente ha montado una respuesta inmunitaria a la proteína en cuestión. Este método además puede usarse a fin de identificar antígenos inmunodominantes o epítopos dentro de

antígenos de proteína.

La eficacia de las composiciones inmunógenas además puede determinarse *in vivo*, mediante la estimulación de modelos animales apropiados del patógeno de la infección de interés.

Las composiciones inmunógenas reveladas en la presente solicitud, en general, se administrarán directamente a un sujeto. El suministro directo puede efectuarse por medio de la inyección parenteral (por ejemplo, por vía subcutánea, intraperitoneal, intravenosa, intramuscular, o al espacio intersticial de un tejido), o la administración mucosal, por ejemplo, por medio de la administración rectal, oral (por ejemplo, comprimido, rocío), vaginal, tópica, transdérmica o transcutánea, intranasal, ocular, auricular, pulmonar u otras administraciones mucosales.

Las composiciones inmunógenas pueden usarse a fin de producir inmunidad sistémica o mucosal, preferentemente, para producir una mejor inmunidad sistémica o mucosal.

Preferentemente, la mejor inmunidad sistémica o mucosal se refleja en una mejor respuesta inmunitaria TH1 o TH2. Preferentemente, la mejor respuesta inmunitaria incluye un incremento en la producción de IgG1, IgG2a o IgA.

La dosificación puede ser mediante un programa de dosis única o un programa de dosis múltiples. Las dosis múltiples pueden usarse en un programa de inmunización primaria o en un programa de inmunización de refuerzo. En un programa de múltiples dosis, las diversas dosis pueden suministrarse por las mismas o diferentes vías; por ejemplo, una primera dosis parenteral y un refuerzo mucosal; una primera dosis mucosal y un refuerzo parenteral, etc. Las múltiples dosis habitualmente se administrarán por lo menos con un intervalo de 1 semana (por ejemplo, aproximadamente 2 semanas, aproximadamente 3 semanas, aproximadamente 4 semanas, aproximadamente 6 semanas, aproximadamente 8 semanas, aproximadamente 10 semanas, aproximadamente 12 semanas,

aproximadamente 16 semanas, etc.).

Las composiciones inmunógenas reveladas en la presente solicitud que incluyen uno o más antígenos o que se usan en conjunto con uno o más antígenos pueden usarse a fin de tratar tanto niños como adultos. En consecuencia, un sujeto humano puede tener menos de 1 año de edad, 1–5 años de edad, 5–15 años de dad, 15–55 años de dad, o por lo menos 55 años de edad. Los sujetos preferidos para recibir dichas composiciones inmunógenas son los ancianos (por ejemplo, > 50 años de edad, > 60 años de edad, y preferentemente, >65 años), los jóvenes (por ejemplo, < 5 años de edad), los pacientes internados, trabajadores de la salud, personal militar y del ejército, mujeres embarazadas, los pacientes con enfermedades crónicas, o los pacientes inmunodeprimidos. Sin embargo, las composiciones inmunógenas no son adecuadas solamente para estos grupos, y pueden usarse más generalmente en la población.

Las composiciones inmunógenas reveladas en la presente solicitud que incluyen uno o más antígenos o que se usan en conjunto con uno o más antígenos pueden administrarse a pacientes sustancialmente al mismo tiempo (por ejemplo, durante la misma consulta médica o visita al médico o centro de vacunación) que otras vacunas, por ejemplo, sustancialmente al mismo tiempo que la vacuna contra el sarampión, la vacuna contra las paperas, vacuna contra la rubéola, vacuna MMR, vacuna contra la varicela, vacuna MMRV, vacuna contra la difteria, vacuna antitetánica, vacuna antitosferínica, vacuna DPT, vacuna conjugada contra *H influenzae* tipo b, una vacuna antipoliomelítica inactivada, una vacuna contra el virus de la hepatitis B, una vacuna conjugada meningocócica (tal como una vacuna tetravalente A C W135 Y), una vacuna contra el virus sincitial respiratorio, etc.

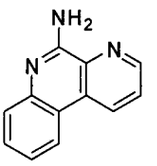
Ejemplos.

Los siguientes ejemplos se ofrecen a fin de ilustrar, y no de limitar, los compuestos de la Fórmula (I) que se proveen en esta invención, y la preparación de dichos compuestos.

Preparación de análogos de benzo[f][1,7]naftiridin–5–amina.

Ejemplo 1.

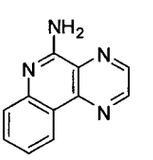
Benzo[f][1,7]naftiridin–5–amina.



Una solución de ácido 2–(*ter*–butoxicarbonilamino)fenilbórico (1,0 eq.) y 3–bromopicolino–nitrilo (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Las dos fases se separaron, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de obtener un sólido de color blanco. ^{1}H RMN (acetona *d*–6): δ 9,04 (d, 1H), 8,91 (d, 1H), 8,45 (d, 1H), 7,86 (dd, 1H), 7,53–7,62 (m, 2H), 7,35 (t, 1H), 6,65 (br, 2H). LRMS [M + H] = 196,1.

Ejemplo 2.

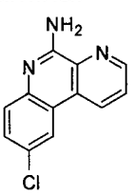
Pirazino[2,3–c]quinolin–5–amina.



Una solución de ácido 2–(*ter*–butoxicarbonilamino)fenilbórico (1,0 eq.) y 3–cloropirazina–2–carbonitrilo (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5 % en moles) y solución acuosa de carbonato de sodio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Las dos fases se separaron, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–50% de acetato de etilo en hexano, a fin de obtener un sólido. ^{1}H RMN (acetona *d*–6): δ 9,14 (s, 1H), 8,95 (s, 1H), 8,77 (d, 1H), 7,63–7,66 (m, 2H), 7,38 (t, 1H), 6,77 (br, 2H), LRMS [M + H] = 197,1.

Ejemplo 3.

9–Clorobenzo[f][1,7]naftiridin–5–amina.



Etapa 1: ter–butil 2–bromo–4–clorofenilcarbamato.

A una solución de 2–bromo–4–cloroanilina (1,0 eq.) en tetrahidrofurano (0,2 M) a 0°C en atmósfera de N_2 se agregó, por goteo, NaHMDS, 1 M (2,5 eq.). La reacción se agitó durante 15 minutos a 0°C, y se agregó una solución de di–*ter*–butil dicarbonato en tetrahidrofurano. La reacción se calentó hasta temperatura ambiente durante la noche. Se evaporó el solvente, y el residuo resultante se apagó con solución acuosa de HCl, 0,1 N. La suspensión acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema

COMBIFLASH® (ISCO) usando 0–5% de acetato de etilo en hexano a fin de obtener el producto en forma de un aceite de color amarillo.

Etapa 2: ter–butil 4–cloro–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenil–carbamato.

Se mezclaron *ter*–butil 2–bromo–4–clorofenilcarbamato (de la etapa 1) (1,0 eq.), 4,4,4',4',5,5,5',5'–octametil–2,2'–bi(1,3,2–dioxaborolano) (1,5 eq.), dicloro[1,1'–bis(difenilfosfino)ferroceno]paladio (II) (5%) y acetato de sodio (4,5 eq.) en dioxano (0,2 M) en atmósfera de N_2. La reacción se calentó hasta 100°C y se agitó durante la noche. La suspensión resultante se enfrió hasta temperatura ambiente, se diluyó con éter, se filtró a través de celite, y el filtrado se concentró al vacío. La mezcla bruta se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–10% de acetato de etilo en hexano, a fin de lograr *ter*–butil 4–cloro–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenil–carbamato.

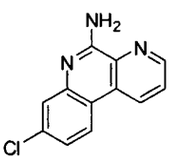
Etapa 3: 9–clorobenzo[f][1,7]naftiridin–5–amina.

Una solución de *ter*–butil 4–cloro–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenil–carbamato (de la etapa 2) (1,0 eq.) y 3–bromopicolino–nitrilo (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Las dos fases se separaron, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–50% de acetato de etilo en hexano, y luego, se repurificó usando 0–5% de metanol en diclorometano

a fin de obtener un sólido. ^{1}H RMN (acetona *d*–6): δ 9,08 (d, 1H), 8,96 (d, 1H), 8,45 (s, 1H), 7,86–7,89 (dd, 1H), 7,60 (d, 1H), 7,54 (d, 1H), 6,78 (br, 2H). LRMS [M + H] = 230,1.

Ejemplo 4.

8–Clorobenzo[f][1,7]naftiridin–5–amina.



Etapa 1: ter–butil 2–bromo–5–clorofenilcarbamato.

A una solución de 2–bromo–5–cloroanilina (1,0 eq.) en tetrahidrofurano (0,2 M) a 0°C en atmósfera de N_2 se agregó, por goteo, NaHMDS, 1 M (2,5 eq.). La reacción se agitó durante 15 minutos a 0°C, y se agregó una solución de di–*ter*–butil dicarbonato en tetrahidrofurano. La reacción se entibió hasta temperatura ambiente durante la noche. Se evaporó el solvente, y el residuo resultante se apagó con solución acuosa de HCl, 0,1 N. La suspensión acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de acetato de etilo en hexano, a fin de obtener el producto en forma de un aceite de color amarillo claro.

Etapa 2: ter–butil 5–cloro–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenil–carbamato.

Se mezclaron *ter*–butil 2–bromo–5–clorofenilcarbamato (de la etapa 1) (1,0 eq.), 4,4,4',4',5,5,5',5'–octametil–2,2'–bi(1,3,2–dioxaborolano) (1,5 eq.), dicloro[1,1'–bis(difenilfosfino)ferroceno]paladio (II) (5%) y acetato de sodio (4,5 eq.) en dioxano (0,2 M) en atmósfera de N_2. La reacción se calentó hasta 100°C y se agitó durante la noche. La suspensión resultante se enfrió hasta temperatura ambiente, se diluyó con éter, se filtró a través de celite, y el filtrado se concentró al

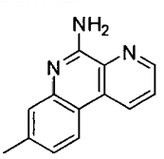
vacío. La mezcla bruta se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de acetato de etilo en hexano, a fin de obtener *ter*–butil 5–cloro–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenil–carbamato.

Etapa 3: 8–clorobenzo[f][1,7]naftiridin–5–amina.

Una solución de *ter*–butil 5–cloro–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenil–carbamato (de la etapa 2) (1,0 eq.) y 3–bromopicolino–nitrilo (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de metanol en diclorometano, a fin de obtener un sólido semipuro, que luego se agitó en 10% de acetato de etilo caliente en hexano, se filtró y se secó de manera de obtener un sólido puro. ^{1}H RMN (acetona *d*–6): δ 9,03 (d, 1H), 8,93 (d, 1H), 8,46 (d, 1H), 7,85–7,88 (dd, 1H), 7,57 (s, 1H), 7,32 (d, 1H), 6,94 (br, 2H). LRMS [M + H] = 230,1.

Ejemplo 5.

8–Metilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: ter–butil 2–bromo–5–metilfenilcarbamato.

A una solución de 2–bromo–5–metilanilina (1,0 eq.) en tetrahidrofurano (0,2

M) a 0°C en atmósfera de N_2 se agregó, por goteo, NaHMDS, 1 M (2,5 eq.). La reacción se agitó durante 15 minutos a 0°C, y se agregó una solución de di–*ter*–butil dicarbonato en tetrahidrofurano. La reacción se entibió hasta temperatura ambiente durante la noche. Se evaporó el solvente, y el residuo resultante se apagó con solución acuosa de HCl, 0,1 N. La suspensión acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro, y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de acetato de etilo en hexano, a fin de obtener el producto en forma de un aceite de color amarillo claro.

Etapa 2: ter–butil 5–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato.

Se mezclaron *ter*–butil 2–bromo–5–metilfenilcarbamato (de la etapa 1) (1,0 eq.), 4,4,4',4',5,5,5',5'–octametil–2,2'–bi(1,3,2–dioxaborolano) (1,5 eq.), dicloro[1,1'–bis(difenilfosfino)ferroceno]paladio (II) (5%) y acetato de sodio (4,5 eq.) en dioxano (0,2 M) en atmósfera de N_2. La reacción se calentó hasta 100°C y se agitó durante la noche. La suspensión resultante se enfrió hasta temperatura ambiente, se diluyó con éter, se filtró a través de celite, y el filtrado se concentró al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–8% de éter en hexano a fin de obtener *ter*–butil 5–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato.

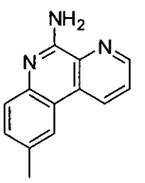
Etapa 3: 8–metilbenzo[f][1,7]naftiridin–5–amina.

Una solución de *ter*–butil 5–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (de la etapa 2) (1,0 eq.) y 3–bromopicolino–nitrilo (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La

reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–40% de acetato de etilo en tolueno, a fin de obtener un sólido puro. ^{1}H RMN (acetona *d*–6): δ 8,98 (d, 1H), 8,87 (d, 1H), 8,32 (d, 1H), 7,79–7,82 (dd, 1H), 7,42 (s, 1H), 7,18 (d, 1H), 6,6 (br, 2H), 2,45 (s, 3H). LRMS [M + H] = 210,1.

Ejemplo 6.

9–Metilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: ter–butil 2–bromo–4–metilfenilcarbamato.

A una solución de 2–bromo–4–metilanilina (1,0 eq.) en tetrahidrofurano (0,2 M) a 0°C en atmósfera de N_2 se agregó, por goteo, NaHMDS, 1 M (2,5 eq.). La reacción se agitó durante 15 minutos a 0°C, y se agregó una solución de di–*ter*–butil dicarbonato en tetrahidrofurano. La reacción se entibió hasta temperatura ambiente durante la noche. Se evaporó el solvente, y el residuo resultante se apagó con solución acuosa de HCl, 0,1 N. La suspensión acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de acetato de etilo en hexano, de manera de obtener el producto en forma de un aceite de color amarillo claro.

Etapa 2: ter–butil 4–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato.

Se mezclaron *ter*–butil 2–bromo–4–metilfenilcarbamato (de la etapa 1) (1,0 eq.), 4,4,4',4',5,5,5',5'–octametil–2,2'–bi(1,3,2–dioxaborolano) (1,5 eq.), dicloro[1,1'–bis(difenilfosfino)ferroceno]paladio (II) (5%) y acetato de sodio (4,5 eq.) en dioxano (0,2 M) en atmósfera de N_2. La reacción se calentó hasta 100°C y se agitó durante la noche. La suspensión resultante se enfrió hasta temperatura ambiente, se diluyó con éter, se filtró a través de celite, y el filtrado se concentró al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–8% de éter en hexano de manera de obtener *ter*–butil 4–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato.

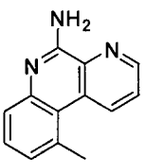
Etapa 3: 9–metilbenzo[f][1,7]naftiridin–5–amina.

Una solución de *ter*–butil 4–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (de la etapa 2) (1,0 eq.) y 3–bromopicolino–nitrilo (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de metanol en diclorometano, a fin de obtener un sólido semipuro, que luego se sometió a torbellino en acetato de etilo caliente, se filtró y se secó de manera de obtener un sólido puro. ^{1}H RMN (acetona *d*–6): δ 9,02 (d, 1H), 8,89 (d, 1H), 8,25 (s, 1H),

7,80–7,84 (dd, 1H), 7,52 (d, 1H), 7,40 (d, 1H), 6,5 (br, 2H), 2,48 (s, 3H). LRMS [M + H] = 210,2.

Ejemplo 7.

10–Metilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: ter–butil 2–bromo–3–metilfenilcarbamato.

A una solución de 2–bromo–3–metilanilina (1,0 eq.) en tetrahidrofurano (0,2 M) a 0°C en atmósfera de N_2 se agregó, por goteo, NaHMDS, 1 M (2,5 eq.). La reacción se agitó durante 15 minutos a 0°C, y se agregó una solución de di–*ter*–butil dicarbonato en tetrahidrofurano. La reacción se entibió hasta temperatura ambiente durante la noche. Se evaporó el solvente, y el residuo resultante se apagó con solución acuosa de HCl, 0,1 N. La suspensión acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de acetato de etilo en hexano a fin de obtener producto en forma de un aceite de color amarillo claro.

Etapa 2: ter–butil 3–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato.

Ter–butil 2–bromo–3–metilfenilcarbamato (de la etapa 1) (1,0 eq.), 4,4,4',4',5,5,5',5'–octametil–2,2'–bi(1,3,2–dioxaborolano) (1,5 eq.), dicloro[1,1'–bis(difenilfosfino)ferroceno]paladio (II) (5%) y acetato de sodio (4,5 eq.) se mezclaron en dioxano (0,2 M) en atmósfera de N_2. La reacción se calentó hasta 100°C y se agitó durante la noche. La suspensión resultante se enfrió hasta temperatura ambiente, se diluyó con éter, se filtró a través de celite, y el filtrado se concentró al vacío. El material bruto se purificó por medio de la cromatografía

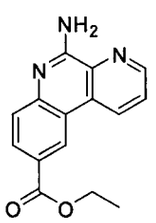
instantánea en un sistema COMBIFLASH® (ISCO) usando 0–10% de éter en hexano hasta lograr *ter*–butil 3–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato.

Etapa 3: 10–metilbenzo[f][1,7]naftiridin–5–amina.

Una solución de *ter*–butil 3–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (de la etapa 2) (1,0 eq.) y 3–bromopicolino–nitrilo (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–40% de acetato de etilo en tolueno de manera de obtener un sólido semipuro, que luego se sometió a torbellino en 10% de acetato de etilo caliente en hexano, se filtró y se secó, a fin de obtener un sólido puro. ^{1}H RMN (acetona *d*–6): δ 9,22 (d, 1H), 8,90 (d, 1H), 7,82–7,85 (dd, 1H), 7,54 (d, 1H), 7,45 (t, 1H), 7,19 (d, 1H), 6,6 (br, 2H), 2,98 (s, 3H), LRMS [M + H] = 210,2.

Ejemplo 8.

Etil 5–aminobenzo[f][1,7]naftiridina–9–carboxilato.



Etapa 1: etil 3–bromo–4–(ter–butoxicarbonilamino)benzoato.

A una solución de 4–amino–3–bromobenzoato (1,0 eq.) en tetrahidrofurano (0,2 M) a 0°C en atmósfera de N_2 se agregó, por goteo, NaHMDS, 1 M (2,5 eq.). La reacción se agitó durante 15 minutos a 0°C, y se agregó una solución de di–*ter*–butil dicarbonato en tetrahidrofurano. La reacción se entibió hasta temperatura ambiente durante la noche. Se evaporó el solvente, y el residuo resultante se apagó con solución acuosa de HCl, 0,1 N. La suspensión acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de acetato de etilo en hexano, a fin de obtener el producto en forma de un aceite de color amarillo claro.

Etapa 2: Etil 4–(ter–butoxicarbonilamino)–3–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)benzoato.

Etil 3–bromo–4–(*ter*–butoxicarbonilamino)benzoato (de la etapa 1) (1,0 eq.), 4,4,4',4',5,5,5',5'–octametil–2,2'–bi(1,3,2–dioxaborolano) (1,5 eq.), dicloro[1,1'–bis(difenilfosfino)ferroceno]paladio (II) (5%) y acetato de sodio (4,5 eq.) se mezclaron en dioxano (0,2 M) en atmósfera de N_2. La reacción se calentó hasta 100°C y se agitó durante la noche. La suspensión resultante se enfrió hasta temperatura ambiente, se diluyó con éter, se filtró a través de celite, y el filtrado se concentró al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–10% de éter en hexano, de manera de obtener etil 4–(*ter*–butoxicarbonilamino)–3–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)benzoato.

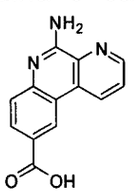
Etapa 3: etil 5–aminobenzo[f][1,7]naftiridina–9–carboxilato.

Una solución de etil 4–(*ter*–butoxicarbonilamino)–3–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)benzoato (de la etapa 2) (1,0 eq.) y 3–bromopicolino–

nitrilo (1,0 eq.) en tolueno/etanol (10:1, 0,23 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y carbonato de potasio anhidro (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–40% de acetato de etilo en tolueno, a fin de obtener un sólido semipuro, que luego se sometió a torbellino en 10% de acetato de etilo caliente en hexano, se filtró y se secó a fin de lograr un sólido puro. ^{1}H RMN (acetona *d*–6): δ 9,11 (d, 1H), 9,05 (s, 1H), 8,95 (d, 1H), 8,14 (d, 1H), 7,89–7,92 (dd, 1H), 7,63 (d, 1H), 4,38 (q, 2H), 1,40 (t, 3H). LRMS [M + H] = 268,2.

Ejemplo 9.

Ácido 5–aminobenzo[f][1,7]naftiridina–9–carboxílico.

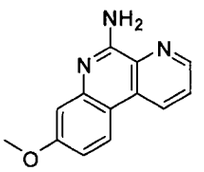


Etil 5–aminobenzo[f][1,7]naftiridina–9–carboxilato (Ejemplo 8) (1,0 eq.) se mezcló con NaOH, 1 N (2,0 eq.) en etanol (0,12 M). La reacción se calentó hasta 80°C y se agitó durante 36 horas. Se eliminó el solvente al vacío. El residuo se suspendió en agua, y se ajustó el pH a neutro usando solución acuosa de ácido cítrico al 5%. La suspensión se centrifugó (2500 r. p. m., 5 min), y se eliminó el sobrenadante. Los sólidos resultantes se resuspendieron en agua mediante el torbellino, se centrifugaron (2500 r. p. m., 5 min), y se eliminó el sobrenadante. Se repitieron las etapas de resuspensión, centrifugación y eliminación del sobrenadante, con metanol caliente, acetato de etilo caliente, y éter, a fin de

obtener un sólido puro. ^{1}H RMN (DMSO): δ 12,86 (s, 1H), 9,15 (d, 1H), 9,00 (s, 1H), 8,97 (d, 1H), 8,07 (d, 1H), 7,88–7,91 (dd, 1H), 7,56–7,59 (m, 3H). LRMS [M + H] = 240,1.

Ejemplo 10.

8–Metoxibenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 2–bromo–5–metoxianilina.

Una solución de 1–bromo–4–metoxi–2–nitrobenceno (1,0 eq.), polvo de hierro (3,0 eq.) y HCl concentrado (1,04 eq.) se mezcló en etanol (0,64 M) y se calentó hasta reflujo. La reacción se agitó durante 24 horas, y se evaporó el solvente. El residuo resultante se diluyó con acetato de etilo y solución acuosa de cloruro de amonio saturado. La capa acuosa se extrajo tres veces con acetato de etilo, y las capas orgánicas combinadas se lavaron con agua, con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–15% de acetato de etilo en hexano, de manera de obtener el producto en forma de un aceite.

Etapa 2: ter–butil 2–bromo–5–metoxifenilcarbamato.

A una solución de 2–bromo–5–metoxianilina (1,0 eq.) (de la etapa 1) en tetrahidrofurano (0,2 M) a 0°C en atmósfera de N_2 se agregó, por goteo, NaHMDS, 1 M (2,5 eq.). La reacción se agitó durante 15 minutos a 0°C, y se agregó una solución de di–*ter*–butil dicarbonato en tetrahidrofurano. La reacción se entibió hasta temperatura ambiente durante la noche. Se evaporó el solvente, y el residuo resultante se apagó con solución acuosa de HCl, 0,1 N. La suspensión acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se

concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de acetato de etilo en hexano, de manera de obtener el producto en forma de un aceite de color amarillo claro.

Etapa 3: ter–butil 5–metoxi–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato.

Ter–butil 2–bromo–5–metoxifenilcarbamato (de la etapa 2) (1,0 eq.), 4,4,4',4',5,5,5',5'–octametil–2,2'–bi(1,3,2–dioxaborolano) (1,5 eq.), dicloro[1,1'–bis(difenilfosfino)ferroceno]paladio (II) (5%) y acetato de sodio (4,5 eq.) se mezclaron en dioxano (0,2 M) en atmósfera de N_2. La reacción se calentó hasta 100°C y se agitó durante la noche. La suspensión resultante se enfrió hasta temperatura ambiente, se diluyó con éter, se filtró a través de celite, y el filtrado se concentró al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–15% de éter en hexano, a fin de obtener *ter*–butil 5–metoxi–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato.

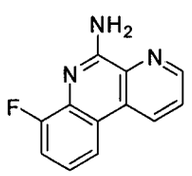
Etapa 4: 8–metoxibenzo[f][1,7]naftiridin–5–amina.

Una solución de *ter*–butil 5–metoxi–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (de la etapa 3) (1,0 eq.) y 3–bromopicolino–nitrilo (1,0 eq.) en tolueno/etanol (10:1, 0,23 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y carbonato de potasio anhidro (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía

instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de metanol en diclorometano a fin de lograr un sólido semipuro, que luego se recristalizó en acetato de etilo, se filtró y se secó de manera de obtener un sólido puro. ^{1}H RMN (acetona *d*–6): δ 8,91 (d, 1H), 8,82 (d, 1H), 8,33 (d, 1H), 7,76–7,79 (dd, 1H), 7,07 (s, 1H), 6,96 (d, 1H), 6,6 (br, 2H), 3,90 (s, 3H). LRMS [M + H] = 226,1.

Ejemplo 11.

7–Fluorbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: ter–butil 2–fluorfenilcarbamato.

A una solución de 2–fluoranilina (1,0 eq.) en tetrahidrofurano (0,2 M) a 0°C en una atmósfera de N_2 se agregó, por goteo, NaHMDS, 1 M (2,5 eq.). La reacción se agitó durante 15 minutes a 0°C, y se agregó una solución de di–*ter*–butil dicarbonato en tetrahidrofurano. La reacción se entibió hasta temperatura ambiente durante la noche. Se evaporó el solvente, y el residuo resultante se apagó con solución acuosa de HCl, 0,1 N. La suspensión acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro, y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de acetato de etilo en hexano, a fin de obtener el producto en forma de un aceite de color amarillo claro.

Etapa 2: ácido 2–(ter–butoxicarbonilamino)–3–fluorfenilbórico.

A una solución de *ter*–butil 2–fluorfenilcarbamato (de la etapa 1) (1,0 eq.) en tetrahidrofurano (0,25 M) a –78°C en una atmósfera de N_2 se agregó, por goteo, *ter*–butil litio, 1,7 M (2,4 eq.). La reacción se entibió hasta –40°C lentamente en un período de tiempo de 2 horas, y se agregó trimetil borato puro

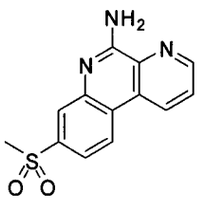
(3,8 eq.). La reacción se entibió hasta temperatura ambiente en un período de tiempo de 30 minutos. Se agregó lentamente una solución acuosa de NaOH, 1 N, a la reacción, y esta se agitó durante 15 minutos. La mezcla se vertió en acetato de etilo y se acidificó con HCl, 3 N, a fin de disolver los sólidos. La capa acuosa se extrajo dos veces con acetato de etilo, y las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. Los sólidos resultantes se agitaron en 1:1 de éter/hexano, se filtraron y se secaron. Los sólidos se llevaron a la siguiente etapa sin otra purificación.

Etapa 3: 7–fluorbenzo[f][1,7]naftiridin–5–amina.

Una solución de ácido 2–(ter–butoxicarbonilamino)–3–fluorfenilbórico (de la etapa 2) (1,0 eq.) y 3–bromopicolino–nitrilo (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5 % en moles) y solución acuosa, 2 N, de carbonato de potasio (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. Después del trabajo, el producto bruto se suspendió en tolueno caliente, se centrifugó (2500 r. p. m., 5 min), y se eliminó el sobrenadante. Se repitieron las etapas de suspensión, centrifugación y eliminación del sobrenadante con acetato de etilo caliente, éter y hexano de manera de obtener un sólido puro. ^1H RMN (acetona *d*–6): δ 9,04 (d, 1H), 8,96 (d, 1H), 8,27 (d, 1H), 7,86–7,90 (dd, 1H), 7,28–7,34 (m, 2H), 6,9 (br, 2H). LRMS [M + H] = 214,1.

Ejemplo 12.

8–(Metilsulfonil)benzo[f][1,7]naftiridin–5–amina.



Etapa 1: 2–bromo–5–(metilsulfonil)anilina.

Una solución de 1–bromo–4–(metilsulfonil)–2–nitrobenceno (1,0 eq.), polvo de hierro (3,0 eq.) y HCl concentrado (1,04 eq.) se mezcló en etanol (0,64 M) y se calentó hasta reflujo. La reacción se agitó durante 24 horas, y se evaporó el solvente. El residuo resultante se diluyó con acetato de etilo y solución de cloruro de amonio acuoso saturado. Se extrajo la capa acuosa tres veces con acetato de etilo, y las capas orgánicas combinadas se lavaron con agua, con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó mediante la trituración con 1:1 de hexano/éter, a fin de obtener un sólido de color amarillo claro.

Etapa 2: ter–butil 2–bromo–5–(metilsulfonil)fenilcarbamato.

A una solución de 2–bromo–5–(metilsulfonil)anilina (de la etapa 1) (1,0 eq.) en tetrahidrofurano (0,2 M) a 0°C en una atmósfera de N_2 se agregó, por goteo, NaHMDS, 1 M (2,5 eq.). La reacción se agitó durante 15 minutos a 0°C, y se agregó una solución de di–*ter*–butil dicarbonato en tetrahidrofurano. La reacción se entibió hasta temperatura ambiente durante la noche. Se evaporó el solvente, y el residuo resultante se apagó con solución acuosa de HCl, 0,1 N. La suspensión acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de acetato de etilo en hexano, a fin de obtener *ter*–butil 2–bromo–5–(metilsulfonil)fenilcarbamato.

Etapa 3: ter–butil 5–(metilsulfonil)–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato.

Ter–butil 2–bromo–5–(metilsulfonil)fenilcarbamato (de la etapa 2) (1,0 eq.), 4,4,4',4',5,5,5',5'–octametil–2,2'–bi(1,3,2–dioxaborolano) (1,5 eq.), dicloro[1,1'–bis(difenilfosfino)ferroceno]paladio (II) (5%) y acetato de sodio (4,5 eq.) se mezclaron en dioxano (0,2 M) en una atmósfera de N_2. La reacción se calentó hasta 100°C y se agitó durante la noche. La suspensión resultante se enfrió hasta temperatura ambiente, se diluyó con éter, se filtró a través de celite, y el filtrado se concentró al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–50% de acetato de etilo en hexano, de manera de obtener un sólido que luego se trituró con 10% de éter/hexano, a fin de obtener *ter*–butil 5–(metilsulfonil)–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato en forma de un sólido de color blanco.

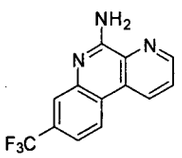
Etapa 4: 8–(metilsulfonil)benzo[f][1,7]naftiridin–5–amina.

Una solución de *ter*–butil 5–(metilsulfonil)–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato(de la etapa 3) (1,0 eq.) y 3–bromopicolino–nitrilo (1,0 eq.) en tolueno (0,24 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (4,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de metanol en diclorometano, de modo de obtener un sólido que luego se trituró con 1:1 de hexano/etil acetato, a fin de lograr 8–(metilsulfonil)benzo[f][1,7]naftiridin–5–amina.

^{1}H RMN (acetona *d*–6): δ 9,16 (d, 1H), 9,03 (d, 1H), 8,71 (d, 1H), 8,11 (s, 1H), 7,93–7,96 (dd, 1H), 7,81 (d, 1H), 7,0 (br, 2H), 3,19 (s, 3H). LRMS [M + H] = 274,1.

Ejemplo 13.

8–(Trifluormetil)benzo[f][1,7]naftiridin–5–amina.



Etapa 1: ter–butil 2–bromo–5–(trifluormetil)fenilcarbamato.

A una solución de 2–bromo–5–(trifluormetil)anilina (1,0 eq.) en tetrahidrofurano (0,2 M) a 0°C en una atmósfera de N_2 se agregó por goteo NaHMDS, 1 M (2,5 eq.). La reacción se agitó durante 15 minutes a 0°C, y se agregó una solución de di–*ter*–butil dicarbonato en tetrahidrofurano. La reacción se entibió hasta temperatura ambiente durante la noche. Se evaporó el solvente, y el residuo resultante se apagó con solución acuosa de HCl, 0,1 N. La suspensión acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de acetato de etilo en hexano, a fin de obtener el producto en forma de un aceite de color amarillo claro.

Etapa 2: ter–butil 2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–5–(trifluormetil)fenilcarbamato.

Ter–butil 2–bromo–5–(trifluormetil)fenilcarbamato (de la etapa 1) (1,0 eq.), 4,4,4',4',5,5,5',5'–octametil–2,2'–bi(1,3,2–dioxaborolano) (1,5 eq.), dicloro[1,1'–bis(difenilfosfino)ferroceno]paladio (II) (5%) y acetato de sodio (4,5 eq.) se mezclaron en dioxano (0,2 M) en una atmósfera de N_2. La reacción se calentó hasta 100°C y se agitó durante la noche. La suspensión resultante se enfrió hasta

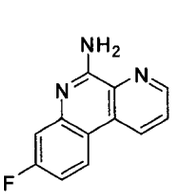
temperatura ambiente, se diluyó con éter, se filtró a través de celite, y el filtrado se concentró al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–10% de éter en hexano, a fin de obtener un producto impuro que se llevó a la siguiente etapa sin otra purificación.

Etapa 3: 8–(trifluormetil)benzo[f][1,7]naftiridin–5–amina.

Una solución de *ter*–butil 2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–5–(trifluormetil)fenilcarbamato (de la etapa 2) (1,0 eq.) y 3–bromopicolino–nitrilo (1,0 eq.) en tolueno (0,24 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (4,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–40% de acetato de etilo en tolueno, a fin de obtener un sólido que se trituró con 10% de acetato de etilo en hexano, para lograr 8–(trifluormetil)benzo[f][1,7]naftiridin–5–amina. ^{1}H RMN (acetona *d*–6): δ 9,13 (d, 1H), 9,00 (d, 1H), 8,67 (d, 1H), 7,91–7,94 (dd, 1H), 7,86 (s, 1H), 7,58 (d, 1H), 6,9 (br, 2H). LRMS [M + H] = 264,1.

Ejemplo 14.

8–Fluorbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: ter–butil 2–bromo–5–fluorfenilcarbamato.

A una solución de 2–bromo–5–fluoranilina (1,0 eq.) en tetrahidrofurano (0,2 M) a 0°C en una atmósfera de N_2 se agregó por goteo NaHMDS, 1 M (2,5 eq.). La reacción se agitó durante 15 minutes a 0°C, y se agregó una solución de di–*ter*–butil dicarbonato en tetrahidrofurano. La reacción se entibió hasta temperatura ambiente durante la noche. Se evaporó el solvente, y el residuo resultante se apagó con solución acuosa de HCl, 0,1 N. La suspensión acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de acetato de etilo en hexano, a fin de lograr el producto en forma de un aceite de color amarillo claro.

Etapa 2: ter–butil 5–fluor–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato.

Ter–butil 2–bromo–5–fluorfenilcarbamato (de la etapa 1) (1,0 eq.), 4,4,4',4',5,5,5',5'–octametil–2,2'–bi(1,3,2–dioxaborolano) (1,5 eq.), dicloro[1,1'–bis(difenilfosfino)ferroceno]paladio (II) (5%) y acetato de sodio (4,5 eq.) se mezclaron en dioxano (0,2 M) en una atmósfera de N_2. La reacción se calentó hasta 100°C y se agitó durante la noche. La suspensión resultante se enfrió hasta temperatura ambiente, se diluyó con éter, se filtró a través de celite, y el filtrado se concentró al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de éter en hexano a fin de obtener el producto en forma de un sólido de color amarillo.

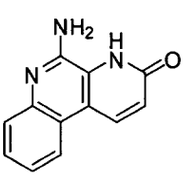
Etapa 3: 8–fluorbenzo[f][1,7]naftiridin–5–amina.

Una solución de *ter*–butil 5–fluor–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (de la etapa 2) (1,0 eq.) y 3–bromopicolino–nitrilo (1,0 eq.) en tolueno (0,24 M) se mezcló con tetraquis(trifenil–fosfina)paladio

(5% en moles) y solución acuosa de carbonato de potasio, 2 N (4,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–40% de acetato de etilo en tolueno, a fin de obtener un sólido que luego se trituró con 10% de acetato de etilo en hexano para lograr 8–fluorbenzo[f][1,7]naftiridin–5–amina. ^{1}H RMN (acetona *d*–6): δ 9,00 (d, 1H), 8,90 (d, 1H), 8,46–8,50 (dd, 1H), 7,83–7,87 (dd, 1H), 7,26 (d, 1H), 7,15 (t, 1H), 6,9 (br, 2H). LRMS [M + H] = 214,1.

Ejemplo 15.

5–Aminobenzo[f][1,7]naftiridin–3(4H)–ona.



Etapa 1: 3–bromo–2–cianopiridina 1–óxido.

A una solución de 3–bromopicolinonitrilo (1,0 eq.) en cloroformo (0,3 M) se agregó ácido meta–cloroperbenzoico (mCPBA) al 77% (1,8 eq.) y se calentó a 60°C durante 2 días. Después de enfriar hasta temperatura ambiente, se agregó $Ca(OH)_2$ (2,5 eq.), y el precipitado resultante se agitó durante 30 minutos. El precipitado se filtró y se lavó con 5% de metanol en diclorometano. El filtrado se lavó con solución acuosa saturada de $NaHCO_3$. La capa acuosa se extrajo varias veces con 3% de metanol en diclorometano. Las capas orgánicas combinadas se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se agitó en hexano caliente/acetato de etilo (1:1), se filtró y se secó a fin de obtener

el producto deseado en forma de un sólido de color blanco.

Etapa 2: 3–bromo–6–oxo–1,6–dihidropiridina–2–carbonitrilo.

Una solución de 3–bromo–2–cianopiridina 1–óxido (de la etapa 1) en anhídrido acético (0,5 M) se calentó a 150°C durante 24 horas. Se enfrió la reacción hasta temperatura ambiente, y el solvente se eliminó al vacío. El residuo se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–90% de acetato de etilo en hexano, de manera de obtener el O–acetato, que se hidrolizó en NaOH, 2 N/metanol (1:1, 0,2 M) a temperatura ambiente durante 2 horas. La mezcla resultante se diluyó con agua y se acidificó con ácido cítrico al 5%. El precipitado de color amarillo pálido se filtró y se lavó con 9:1 de hexano/acetato de etilo y éter a fin de lograr 3–bromo–6–oxo–1,6–dihidropiridina–2–carbonitrilo.

Etapa 3: 3–bromo–6–(ter–butildimetilsililoxi)picolinonitrilo.

Una solución de 3–bromo–6–oxo–1,6–dihidropiridina–2–carbonitrilo (de la etapa 2) (1,0 eq.), ter–butildimetilsililcloruro (TBSCl) (1,8 eq.) e imidazol (2,5 eq.) en DMF (0,2 M) se calentó hasta 60°C y se agitó durante la noche. La mezcla de reacción se diluyó con agua y se extrajo con éter. Las capas orgánicas combinadas se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El residuo se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–20% de acetato de etilo en hexano. a fin de lograr 3–bromo–6–(*ter*–butildimetilsililoxi)picolinonitrilo.

Etapa 4: 3–(ter–butildimetilsililoxi)benzo[f][1,7]naftiridin–5–amina.

Una solución de ácido 2–(*ter*–butoxicarbonilamino)fenilbórico (1,0 eq.) y 3–bromo–6–(*ter*–butildimetilsililoxi)picolinonitrilo (de la etapa 3) (1,0 eq.) en tolueno/etanol (10:1, 0,2 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol

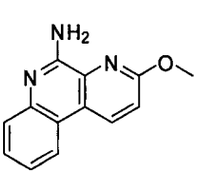
en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–50% de acetato de etilo en hexano, a fin de lograr un sólido.

Etapa 5: 5–aminobenzo[f][1,7]naftiridin–3(4H)–ona.

A una solución de 3–(*ter*–butildimetilsililoxi)benzo[f][1,7]naftiridin–5–amina (de la etapa 4) (1,0 eq.) en tetrahidrofurano (0,05 M) se agregaron fluoruro de tetra–n–butilamonio (TBAF) (1,0 eq.) y ácido acético (1,0 eq.). La reacción se agitó durante 15 minutos, y luego se concentró al vacío. El residuo bruto se suspendió en agua y se neutralizó mediante la adición de solución acuosa saturada de $NaHCO_3$ hasta pH 7. Se filtraron los sólidos, se lavaron con acetona, y se secaron, a fin de lograr 5–aminobenzo[f][1,7]naftiridin–3(4H)–ona. ^{1}H RMN (DMSO *d*–6): δ 8,59 (d, 1H), 8,20 (d, 1H), 7,49 (d, 1H), 7,37–7,41 (dd, 1H), 7,23–7,27 (dd, 1H), 6,88 (br, 2H), 6,79 (d, 1H). LRMS [M + H] = 212,1.

Ejemplo 16.

3–Metoxibenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 3–bromo–6–metoxipicolinonitrilo.

Una solución de 3–bromo–6–oxo–1,6–dihidropiridina–2–carbonitrilo (del Ejemplo 15/Etapa 2) (1,0 eq.), carbonato de plata (1,3 eq.), y yodometano (1,2 eq.) en tolueno (0,2 M) se agitó en la oscuridad a temperatura ambiente durante la noche. El solvente se concentró al vacío, y el residuo resultante se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo

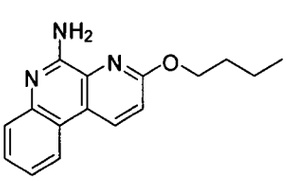
en hexano, a fin de lograr 3–bromo–6–metoxipicolinonitrilo.

Etapa 2: 3–metoxibenzo[f][1,7]naftiridin–5–amina.

Una solución de ácido 2–(*ter*–butoxicarbonilamino)fenilbórico (1,0 eq.) y 3–bromo–6–metoxipicolinonitrilo (de la etapa 1) (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–50% de acetato de etilo en hexano, a fin de lograr 3–metoxibenzo[f][1,7]naftiridin–5–amina en forma de un sólido de color amarillo. ^{1}H RMN (acetona *d*–6): δ 8,91 (d, 1H), 8,34 (d, 1H), 7,63 (d, 1H), 7,51–7,53 (dd, 1H), 7,27–7,33 (m, 2H), 6,65 (br, 2H), 4,11 (s, 3H). LRMS [M + H] = 226,1.

Ejemplo 17.

3–Butoxibenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 3–bromo–6–butoxipicolinonitrilo.

Una solución de 3–bromo–6–oxo–1,6–dihidropiridina–2–carbonitrilo (del Ejemplo 15/Etapa 2) (1,0 eq.), carbonato de potasio (1,3 eq.) y 1–yodobutano (1,2 eq.) en acetona (0,3 M) se agitó a 70°C durante la noche. El solvente se concentró al vacío, y el residuo resultante se recogió en agua y acetato de etilo. La capa acuosa se extrajo con acetato de etilo tres veces. Las capas orgánicas

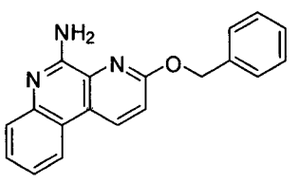
combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–30% de acetato de etilo en hexano, a fin de lograr un sólido incoloro.

Etapa 2: 3–butoxibenzo[f][1,7]naftiridin–5–amina.

Una solución de ácido 2–(*ter*–butoxicarbonilamino)fenilbórico (1,0 eq.) y 3–bromo–6–butoxipicolinonitrilo (de la etapa 1) (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de acetato de etilo en metanol, a fin de lograr 3–butoxibenzo[f][1,7]naftiridin–5–amina en forma de un sólido de color blanco. ^1H RMN (acetona *d*–6): δ 8,91 (d, 1H), 8,34 (d, 1H), 7,61 (d, 1H), 7,48–7,52 (dd, 1H), 7,27–7,33 (m, 2H), 6,51 (br, 2H), 6,55 (t, 2H), 1,81–1,88 (m, 2H), 1,50–1,59 (m, 2H), 1,00 (t, 3H). LRMS [M + H] = 268,1.

Ejemplo 18.

3–(Benciloxi)benzo[f][1,7]naftiridin–5–amina.



Etapa 1: 6–(benciloxi)–3–bromopicolinonitrilo.

Una solución de 3–bromo–6–oxo–1,6–dihidropiridina–2–carbonitrilo (del

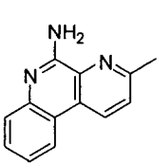
Ejemplo15/Etapa 2) (1,0 eq.), carbonato de plata (1,3 eq.) y bromuro de bencilo (1,2 eq.) en tolueno (0,16 M) se agitó en la oscuridad a 50°C durante la noche. El solvente se concentró al vacío, y el residuo resultante se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–20% de acetato de etilo en hexano, a fin de lograr 6–(benciloxi)–3–bromopicolinonitrilo.

Etapa 2: 3–(benciloxi)benzo[f][1,7]naftiridin–5–amina.

Una solución de ácido 2–(*ter*–butoxicarbonilamino)fenilbórico (1,0 eq.) y 6–(benciloxi)–3–bromopicolinonitrilo (de la etapa 1) (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5 % en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–50% de acetato de etilo en hexano, a fin de lograr 3–(benciloxi)benzo[f][1,7]naftiridin–5–amina en forma de un sólido de color amarillo. ^{1}H RMN (acetona *d*–6): δ 8,95 (d, 1H), 8,35 (d, 1H), 7,58–7,63 (m, 2H), 7,49–7,53 (dd, 1H), 7,30–7,44 (m, 5H), 6,61 (br, 2H), 5,64 (s, 2H). LRMS [M + H] = 302,1.

Ejemplo 19.

3–Metilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 5–bromo–2–metilpiridina 1–óxido.

A una solución de 5–bromo–2–metilpiridina (1,0 eq.) en cloroformo (0,38 M)

se agregó ácido meta–cloroperbenzoico al 77% (mCPBA) (4,0 eq.) y se calentó a 60°C durante 20 horas. Después de enfriar hasta temperatura ambiente, se agregó $Ca(OH)_2$ (5,3 eq.), y el precipitado resultante se agitó durante 30 minutos. El precipitado se filtró y se lavó con 3:1 de $CHCl_3$/metanol. El filtrado se concentró al vacío de manera de obtener un sólido, que se agitó en 30% de acetato de etilo en hexano y se filtró a fin de lograr el N–óxido deseado. El filtrado se concentró al vacío, y el residuo se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–100% de acetato de etilo en hexano, a fin de lograr más del N–óxido deseado. Los dos lotes se combinaron y se llevaron a la siguiente etapa.

Etapa 2: 3–bromo–6–metilpicolinonitrilo.

A una solución de 5–bromo–2–metilpiridina 1–óxido (de la etapa 1) (1,0 eq.) en acetonitrilo (0,2 M) se agregaron cianuro de trimetilsililo (TMSCN) (4,0 eq.) y trietilamina (3,0 eq.). La reacción se calentó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, el solvente se concentró al vacío, y el residuo se purificó por medio de un sistema Combiflash® (ISCO) usando 0–50% de acetato de etilo en hexano, a fin de lograr 3–bromo–6–metilpicolinonitrilo.

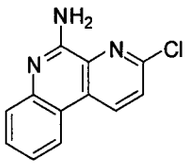
Etapa 3: 3–metilbenzo[f][1,7]naftiridin–5–amina.

Una solución de ácido 2–(*ter*–butoxicarbonilamino)fenilbórico (1,0 eq.) y 3–bromo–6–metilpicolinonitrilo (de la etapa 2) (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH®

(ISCO) usando 0–70% de acetato de etilo en hexano, a fin de lograr 3–metilbenzo[f][1,7]naftiridin–5–amina en forma de un sólido de color amarillo. ^{1}H RMN (metanol *d*–4): δ 8,85 (d, 1H), 8,38 (d, 1H), 7,72 (d, 1H), 7,53–7,61 (m, 2H), 7,34–7,38 (dd, 1H), 2,76 (s, 3H). LRMS [M + H] = 210,1.

Ejemplo 20.

3–Clorobenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 5–bromo–2–cloropiridina 1–óxido.

A una solución de 5–bromo–2–cloropiridina (1,0 eq.) en cloroformo (0,38 M) se agregó ácido meta–cloroperbenzoico al 77% (mCPBA) (4,0 eq.) y se calentó a 60°C durante 20 horas. Después de enfriar hasta temperatura ambiente, se agregó $Ca(OH)_2$ (5,3 eq.), y el precipitado resultante se agitó durante 30 minutos. El precipitado se filtró y se lavó con 3:1 de $CHCl_3$/metanol. El filtrado se concentró al vacío a fin de lograr un sólido, que se agitó en 30% de acetato de etilo en hexano y se filtró, de modo de obtener el N–óxido deseado. El filtrado se concentró al vacío, y el residuo se purificó por medio de un sistema Combiflash® (ISCO) usando 0–100% de acetato de etilo en hexano, a fin de lograr más del N–óxido deseado. Los dos lotes se combinaron y se llevaron a la siguiente etapa.

Etapa 2: 3–bromo–6–cloropicolinonitrilo.

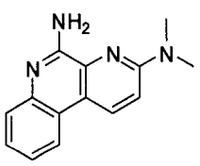
A una solución de 5–bromo–2–cloropiridina 1–óxido (de la etapa 1) (1,0 eq.) en acetonitrilo (0,2 M) se agregaron cianuro de trimetilsililo (TMSCN) (4,0 eq.) y trietilamina (3,0 eq.). La reacción se calentó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, el solvente se concentró al vacío, y el residuo se purificó por medio de un sistema Combiflash® (ISCO) usando 0–40% de acetato de etilo en hexano, a fin de lograr 3–bromo–6–cloropicolinonitrilo.

Etapa 3: 3–clorobenzo[f][1,7]naftiridin–5–amina.

Una solución de ácido 2–(*ter*–butoxicarbonilamino)fenilbórico (1,0 eq.) y 3–bromo–6–cloropicolinonitrilo (de la etapa 2) (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–50% de acetato de etilo en hexano, a fin de lograr un sólido que luego se trituró con 10% de acetato de etilo en hexano, de modo de obtener 3–clorobenzo[f][1,7]naftiridin–5–amina. ^{1}H RMN (acetona *d*–6): δ 9,10 (d, 1H), 8,45 (d, 1H), 7,89 (d, 1H), 7,58–7,65 (m, 2H), 7,35–7,39 (dd, 1H), 6,67 (br, 2H). LRMS [M + H] = 230,1.

Ejemplo 21.

N^3,N^3–Dimetilbenzo[f][1,7]naftiridina–3,5–diamina.

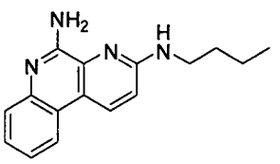


Una solución de 3–clorobenzo[f][1,7]naftiridin–5–amina (Ejemplo 20) (1,0 eq.) se disolvió en 40% de dimetilamina acuosa (0,26 M) y se calentó en un reactor de microondas a 100°C durante 30 minutos. La mezcla de reacción se concentró al vacío, y el residuo se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–90% de acetato de etilo en hexano, a fin de lograr N^3,N^3–dimetilbenzo[f][1,7]naftiridina–3,5–diamina. ^{1}H RMN (metanol *d*–4): δ

8,63 (d, 1H), 8,20 (d, 1H), 7,55 (d, 1H), 7,41–7,45 (dd, 1H), 7,29–7,33 (dd, 1H), 7,27 (d, 1H), 3,26 (s, 6H). LRMS [M + H] = 239,1.

Ejemplo 22.

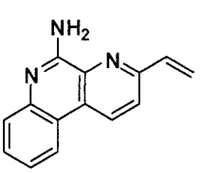
N^3–Butilbenzo[f][1,7]naftiridina–3,5–diamina.



Una solución de 3–clorobenzo[f][1,7]naftiridin–5–amina (Ejemplo 20) (1,0 eq.) se disolvió en *n*–butilamina (0,1 M) y se calentó a 110°C durante la noche. La mezcla de reacción se concentró al vacío, y el residuo se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–90% de acetato de etilo en hexano, a fin de lograr N^3–butilbenzo[f][1,7]naftiridina–3,5–diamina. ^{1}H RMN (metanol *d*–4): δ 8,42 (d, 1H), 8,13 (d, 1H), 7,53 (d, 1H), 7,38–7,42 (dd, 1H), 7,25–7,29 (dd, 1H), 6,96 (d, 1H), 3,48 (t, 2H), 1,63–1,71 (m, 2H), 1,43–1,52 (m, 2H), 0,99 (t, 3H). LRMS [M + H] = 267,2.

Ejemplo 23.

3–Vinilbenzo[f][1,7]naftiridin–5–amina.

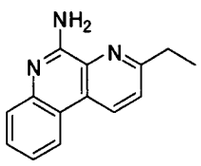


Una solución de 3–clorobenzo[f][1,7]naftiridin–5–amina (Ejemplo 20) (1,0 eq.), 4,4,5,5–tetrametil–2–vinil–1,3,2–dioxaborolano (1,2 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.) en tolueno/etanol (4:1, 0,1 M) se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la

capa acuosa se extrajo con acetato de etilo tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–50% de acetato de etilo en hexano de manera de obtener un sólido, que luego se trituró con 10% de acetato de etilo en hexano a fin de lograr 3–vinilbenzo[f][1,7]naftiridin–5–amina. ^{1}H RMN (acetona *d*–6): δ 8,99 (d, 1H), 8,42 (d, 1H), 8,01 (d, 1H), 7,53–7,62 (m, 2H), 7,30–7,35 (dd, 1H), 7,03–7,10 (dd, 1H), 6,77 (br, 2H), 6,56 (d, 1H), 5,66 (d, 1H). LRMS [M + H] = 222,1.

Ejemplo 24.

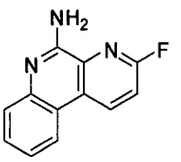
3–Etilbenzo[f][1,7]naftiridin–5–amina.



A una solución de 3–vinilbenzo[f][1,7]naftiridin–5–amina (Ejemplo 23) en acetato de etilo/etanol (1:1, 0,07 M) se agregó 10% en peso de paladio sobre carbón (0,2 eq.). Se introdujo gas hidrógeno por medio de un balón, y la reacción se agitó durante la noche. La mezcla se filtró a través de una almohadilla de celite, lavando con diclorometano. El filtrado se concentró al vacío, para proporcionar 3–etilbenzo[f][1,7]naftiridin–5–amina en forma de un sólido de color blanco. ^{1}H RMN (acetona *d*–6): δ 8,93 (d, 1H), 8,41 (d, 1H), 7,76 (d, 1H), 7,61 (d, 1H), 7,51–7,55 (dd, 1H), 7,30–7,34 (dd, 1H), 6,55 (br, 2H), 6,03 (q, 2H), 1,41 (t, 3H). LRMS [M + H] = 224,1.

Ejemplo 25.

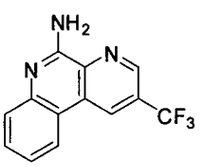
3–Fluorbenzo[f][1,7]naftiridin–5–amina.



Una solución de 3–clorobenzo[f][1,7]naftiridin–5–amina (Ejemplo 20) (1,0 eq.), fluoruro de potasio (3,0 eq.) y 18–corona–6 (0,2 eq.) en N–metilpirrolidona (NMP) (0,4 M) se calentó en un reactor de microondas a 210°C durante 80 minutos. Después de enfriar hasta temperatura ambiente, la mezcla de reacción bruta se purificó por medio de la HPLC usando 10–50% de acetonitrilo en agua, a fin de lograr 3–fluorbenzo[f][1,7]naftiridin–5–amina. ^{1}H RMN (acetona *d*–6): δ 11,40 (br, 2H), 9,38–9,42 (dd, 1H), 8,60 (d, 1H), 7,89–7,92 (dd, 1H), 7,81–7,83 (m, 2H), 7,59–7,66 (m, 1H). LRMS [M + H] = 214,1.

Ejemplo 26.

2–(Trifluormetil)benzo[f][1,7]naftiridin–5–amina.



Etapa 1: 3–cloro–5–(trifluormetil)picolinaldehído oxima.

Una solución de 3–cloro–5–(trifluormetil)picolinaldehído (1,0 eq.), clorhidrato de hidroxilamina (5,0 eq.) y piridina (4,0 eq.) en etanol se calentó hasta 95°C y se agitó durante 1 hora. La reacción se enfrió hasta temperatura ambiente y se diluyó con acetato de etilo y agua. La capa orgánica se lavó con salmuera, con agua, se secó sobre $MgSO_4$ anhidro y se concentró al vacío, a fin de lograr un sólido que se llevó a la siguiente etapa sin otra purificación.

Etapa 2: 3–cloro–5–(trifluormetil)picolinonitrilo.

Una solución de 3–cloro–5–(trifluormetil)picolinaldehído oxima (1,0 eq.) y reactivo de Burgess (1,5 eq.) en tetrahidrofurano (0,5 M) se calentó hasta 65°C y se agitó durante 1 hora. La reacción se enfrió hasta temperatura ambiente y se diluyó con acetato de etilo y agua. La capa orgánica se lavó con agua, con

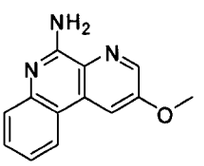
salmuera, se secó sobre $MgSO_4$ anhidro y se concentró al vacío, a fin de lograr un sólido que se llevó a la siguiente etapa sin otra purificación.

Etapa 3: 2–(trifluormetil)benzo[f][1,7]naftiridin–5–amina.

Una solución de ácido 2–(*ter*–butoxicarbonilamino)fenilbórico (1,0 eq.) y 3–cloro–5–(trifluormetil)picolinonitrilo (de la etapa 2) (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–50% de acetato de etilo en hexano, a fin de lograr 2–(trifluormetil)benzo[f][1,7]naftiridin–5–amina. ^{1}H RMN (acetona *d*–6): δ 9,44 (s, 1H), 9,20 (s, 1H), 8,65–8,63 (d, 1H), 7,70–7,61 (m, 2H), 7,44–7,36 (m, 1H), 6,84 (br, 2H). LRMS [M + H] = 264,2.

Ejemplo 27.

2–Metoxibenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 3–cloro–5–metoxipicolinonitrilo.

A una solución de 3,5–dicloropicolinonitrilo (1,0 eq.) en dimetil formamida (DMF) (0,5 M) se agregó metóxido de sodio (1,5 eq.), y la mezcla se calentó hasta 75°C. Después de agitar durante 14 horas, la reacción se diluyó con acetato de etilo y agua. La capa orgánica se lavó con $NaHCO_3$ acuoso saturado tres veces,

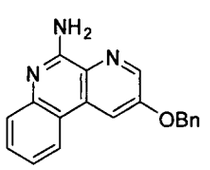
con agua, dos veces, se secó sobre $MgSO_4$ anhidro y se concentró al vacío. El residuo bruto se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 15% de acetato de etilo en hexano, a fin de lograr una mezcla de dos regioisómeros metoxi, uno de los cuales fue el producto deseado. La mezcla se llevó a la siguiente etapa sin otra purificación.

Etapa 2: 2–metoxibenzo[f][1,7]naftiridin–5–amina.

Una solución de ácido 2–(*ter*–butoxicarbonilamino)fenilbórico (1,0 eq.) y 3–cloro–5–metoxipicolinonitrilo (de la etapa 1) (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 50–100% de acetato de etilo en hexano, a fin de lograr 2–metoxibenzo[f][1,7]naftiridin–5–amina.

Ejemplo 28.

2–(Benciloxi)benzo[f][1,7]naftiridin–5–amina.



Etapa 1: 3–(benciloxi)–5–bromopiridina.

Una solución de 5–bromopiridin–3–ol (1,0 eq.), bromuro de bencilo (1,2 eq.) y carbonato de plata (1,3 eq.) en tolueno (0,1 M) se calentó hasta 50°C y se agitó durante 18 horas. Después de enfriar hasta temperatura ambiente, la mezcla de

reacción se filtró, eluyendo con acetato de etilo. El filtrado se concentró al vacío hasta obtener un residuo, que se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 20% de acetato de etilo en hexano, a fin de lograr 3–(benciloxi)–5–bromopiridina.

Etapa 2: 3–(benciloxi)–5–bromopiridina 1–óxido.

Una solución de 3–(benciloxi)–5–bromopiridina (de la etapa 1) (1,0 eq.) y ácido meta–cloroperbenzoico (mCPBA) (4,0 eq.) en diclorometano (0,1 M) se agitó a temperatura ambiente durante 18 horas. La reacción se apagó con solución acuosa saturada de $NaHCO_3$ y se extrajo con diclorometano tres veces. Las capas orgánicas combinadas se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El residuo bruto se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–100% de acetato de etilo en hexano, a fin de lograr 3–(benciloxi)–5–bromopiridina 1–óxido.

Etapa 3: 5–(benciloxi)–3–bromopicolinonitrilo.

A una solución de 53–(benciloxi)–5–bromopiridina 1–óxido (de la etapa 2) (1,0 eq.) en acetonitrilo (0,2 M) se agregaron cianuro de trimetilsililo (TMSCN) (4,0 eq.) y trietilamina (3,0 eq.). La reacción se calentó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, el solvente se concentró al vacío, y el residuo se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–40% de acetato de etilo en hexano, a fin de lograr una mezcla de dos regioisómeros benzoxi, uno de los cuales fue el producto deseado. La mezcla se llevó a la siguiente etapa sin otra purificación.

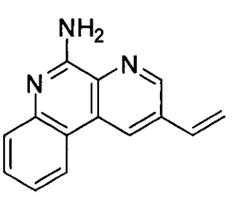
Etapa 4: 2–(benciloxi)benzo[f][1,7]naftiridin–5–amina.

Una solución de ácido 2–(*ter*–butoxicarbonilamino)fenilbórico (1,0 eq.) y 5–(benciloxi)–3–bromopicolinonitrilo (de la etapa 3) (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó

durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con 2% de metanol en diclorometano y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de metanol en diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 50–100% de acetato de etilo en hexano, a fin de lograr 2–(benciloxi)benzo[f][1,7]naftiridin–5–amina. ^{1}H RMN (acetona *d*–6): δ 8,36 (s, 1H), 7,86 (s, 1H), 7,59–7,56 (d, 2H), 7,46–7,42 (dd, 2H), 7,40–7,37 (d, 1H), 7,20–7,15 (dd, 1H), 7,12–7,09 (d, 1H), 6,88–6,86 (d, 1H), 6,77–6,73 (dd, 1H), 5,51 (s, 2H), 4,74 (br, 2H). LRMS [M + H] = 302,3.

Ejemplo 29.

2–Vinilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 3–cloro–5–vinilpicolinonitrilo.

Una solución de 3,5–dicloropicolinonitrilo (1,0 eq.), 4,4,5,5–tetrametil–2–vinil–1,3,2–dioxaborolano (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (3,4 eq.), en tolueno/etanol (2:1, 0,04 M), se agitó a 95°C durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO)

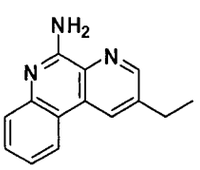
usando 0–80% de acetato de etilo en hexano, a fin de lograr un sólido de color blanco.

Etapa 2: 2–vinilbenzo[f][1,7]naftiridin–5–amina.

Una solución de ácido 2–(*ter*–butoxicarbonilamino)fenilbórico (1,0 eq.) y 3–cloro–5–vinilpicolinonitrilo (de la etapa 1) (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (2,0 eq.), en tolueno/etanol (2:1, 0,03 M), se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con metanol. Los sólidos insolubles se separaron mediante la filtración, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr 2–vinilbenzo[f][1,7]naftiridin–5–amina en forma de un sólido de color amarillo. ^{1}H RMN (metanol–*d*4 – $CDCl_3$): δ 8,87 (d, 1H), 8,69 (d, 1H), 8,28 (d, 1H), 7,49–7,58 (m, 2H), 7,32 (dt, 1H), 6,90 (dd, 1H), 6,09 (d, 1H), 5,54 (d, 1H). LRMS [M + H] = 222,1.

Ejemplo 30.

2–Etilbenzo[f][1,7]naftiridin–5–amina.

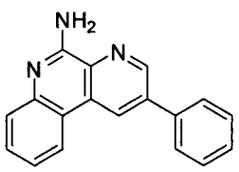


A una solución de 2–vinilbenzo[f][1,7]naftiridin–5–amina (Ejemplo 29) en acetato de etilo/metanol (1:4, 0,05 M) se agregó 10% en peso de paladio sobre carbón (0,2 eq.). Se introdujo gas hidrógeno por medio de un balón, y la reacción se agitó durante 3 horas. La mezcla se filtró a través de una almohadilla de celite, lavando con diclorometano. El filtrado se concentró al vacío y se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo

en hexano, a fin de lograr 2–etilbenzo[f][1,7]naftiridin–5–amina en forma de un sólido. ^{1}H RMN (metanol–d4): δ 8,78–8,81 (m, 2H), 8,45 (d, 1H), 7,55 – 7,63 (m, 2H), 7,35 – 7,40 (m, 1H), 2,97 (q, 2H), 1,43 (t, 2H). LRMS [M + H] = 224,1.

Ejemplo 31.

2–Fenilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 3–cloro–5–fenilpicolinonitrilo.

Una solución de 3,5–dicloropicolinonitrilo (1,0 eq.), 4,4,5,5–tetrametil–2–fenil–1,3,2–dioxaborolano (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (3,4 eq.), en tolueno/etanol (2:1, 0,04 M) se agitó a 100°C durante 2 horas, luego, a 80°C durante 4 horas. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr un sólido de color blanco.

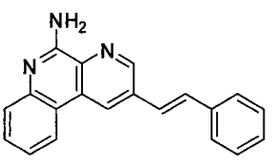
Etapa 2: 2–fenilbenzo[f][1,7]naftiridin–5–amina.

Una solución de ácido 2–(*ter*–butoxicarbonilamino)fenilbórico (1,0 eq.) y 3–cloro–5–fenilpicolinonitrilo (de la etapa 1) (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (2,0 eq.), en tolueno/etanol (2:1, 0,03 M) se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con metanol. Los sólidos insolubles se separaron mediante la filtración, y el filtrado se

concentró al vacío de modo de obtener un residuo bruto. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr 2–fenilbenzo[f][1,7]naftiridin–5–amina en forma de un sólido de color blanco. ^{1}H RMN (dmso–d6): δ 9,13 (d, 1H), 9,03 (d, 1H), 8,56 (d, 1H), 7,98 (d, 2H), 7,43–7,56 (m, 5H), 7,27 (m, 1H), 7,13 (bs, 2H). LRMS [M + H] = 272,2.

Ejemplo 32.

(E)–2–estirilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: (E)–3–cloro–5–estirilpicolinonitrilo.

Una solución de 3,5–dicloropicolinonitrilo (1,0 eq.), (E)–4,4,5,5–tetrametil–2–estiril–1,3,2–dioxaborolano (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (3,4 eq.), en tolueno/etanol (2:1, 0,04 M) se agitó a 100°C durante 2 horas, luego, a 80°C durante 4 horas. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr un sólido de color blanco.

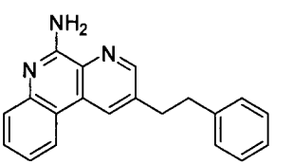
Etapa 2: (E)–2–estirilbenzo[f][1,7]naftiridin–5–amina.

Una solución de ácido 2–(ter–butoxicarbonilamino)fenilbórico (1,0 eq.) y (E)–3–cloro–5–estirilpicolinonitrilo (de la etapa 1) (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (2,0

eq.), en tolueno/etanol (2:1, 0,03 M), se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con metanol. Los sólidos insolubles se separaron mediante la filtración, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr (E)–2–estirilbenzo[f][1,7]naftiridin–5–amina en forma de un sólido de color marrón. ^{1}H RMN (dmso–d6): δ 9,22 (d, 1H), 9,06 (d, 1H), 8,51 (d, 1H), 7,78 (d, 1H), 7,66 (d, 2H), 7,46– 7,56 (m, 3H), 7,70 (t, 2H), 7,26– 7,32 (m, 2H), 7,08 (bs, 2H). LRMS [M + H] = 298,2.

Ejemplo 33.

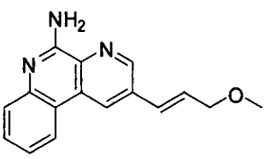
2–Fenetilbenzo[f][1,7]naftiridin–5–amina.



A una solución de (E)–2–estirilbenzo[f][1,7]naftiridin–5–amina (Ejemplo 32) en acetato de etilo/metanol (1:4, 0,05 M) se agregó 10% en peso de paladio sobre carbón (0,2 eq.). Se introdujo gas hidrógeno por medio de un balón, y la reacción se agitó durante 3 horas. La mezcla se filtró a través de una almohadilla de celite, lavando con diclorometano. El filtrado se concentró al vacío, y el producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano a fin de lograr 2–fenetilbenzo[f][1,7]naftiridin–5–amina en forma de un sólido de color amarillo. ^{1}H RMN ($CDCl_3$): δ 8,54 (d, 1H), 8,32 (d, 1H), 8,10 (dd, 1H), 7,63 (dd, 1H), 7,51 (m, 1H), 7,03 – 7,32 (m, 6H), 6,16 (bs, 2H), 3,11 (t, 2H), 2,97 (t, 2H). LRMS [M + H] = 300,1.

Ejemplo 34.

(E)–2–(3–Metoxiprop–1–enil)benzo[f][1,7]naftiridin–5–amina.



Etapa 1: (E)–3–cloro–5–(3–metoxiprop–1–enil)picolinonitrilo.

Una solución de 3,5–dicloropicolinonitrilo (1,0 eq.), (E)–2–(3–metoxiprop–1–enil)–4,4,5,5–tetrametil–1,3,2–dioxaborolano (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (3,4 eq.), en tolueno/etanol (2:1, 0,04 M), se agitó a 100°C durante 2 horas, luego, a 80°C durante 4 horas. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr (E)–3–cloro–5–(3–metoxiprop–1–enil)picolinonitrilo en forma de un sólido de color blanco.

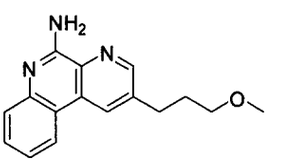
Etapa 2: (E)–2–(3–metoxiprop–1–enil)benzo[f][1,7]naftiridin–5–amina.

Una solución de ácido 2–(*ter*–butoxicarbonilamino)fenilbórico (1,0 eq.) y (E)–3–cloro–5–(3–metoxiprop–1–enil)picolinonitrilo (de la etapa 1) (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (2,0 eq.), en tolueno/etanol (2:1, 0,03 M), se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con metanol. Los sólidos insolubles se separaron mediante la filtración, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El producto bruto se purificó por medio de la cromatografía instantánea en un

sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano a fin de lograr (E)–2–(3–metoxiprop–1–enil)benzo[f][1,7]naftiridin–5–amina en forma de un sólido de color amarillo. ^{1}H RMN (dmso–d6): δ 9,24 (d, 1H), 9,18 (d, 1H), 8,54 (d, 1H), 7,52– 7,58 (m, 2H), 7,31 (m, 1H), 7,11 (bs, 2H), 6,86 – 7,00 (m, 2H), 4,18 (d, 2H), 3,36 (s, 3H). LRMS [M + H] = 266,2.

Ejemplo 35.

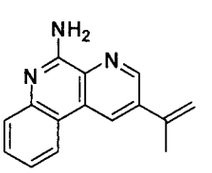
2–(3–Metoxipropil)benzo[f][1,7]naftiridin–5–amina.



A una solución de (E)–2–(3–metoxiprop–1–enil)benzo[f][1,7]naftiridin–5–amina (Ejemplo 34) en acetato de etilo/metanol (1:4, 0,05 M) se agregó 10% en peso de paladio sobre carbón (0,2 eq.). Se introdujo gas hidrógeno por medio de un balón, y la reacción se agitó durante 3 horas. La mezcla se filtró a través de una almohadilla de celite, lavando con diclorometano. El filtrado se concentró al vacío, y el producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr 2–(3–metoxipropil)benzo[f][1,7]naftiridin–5–amina como un sólido de color blanco. ^{1}H RMN ($CDCl_3$): δ 8,64 (d, 1H), 8,46 (d, 1H), 8,19 (d, 1H), 7,66 (d, 1H), 7,53 (m, 1H), 7,31 (m, 1H), 6,56 (bs, 2H), 3,37 (t, 2H), 3,31 (s, 3H), 2,91 (t, 2H), 1,93 – 2,00 (m, 2H). LRMS [M + H] = 268,1.

Ejemplo 36.

2–(Prop–1–en–2–il)benzo[f][1,7]naftiridin–5–amina.



Etapa 1: 3–cloro–5–(prop–1–en–2–il)picolinonitrilo.

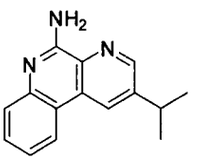
Una solución de 3,5–dicloropicolinonitrilo (1,0 eq.), 4,4,5,5–tetrametil–2–(prop–1–en–2–il)–1,3,2–dioxaborolano (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (3,4 eq.) en tolueno/etanol (2:1, 0,04 M) se agitó a 100°C durante 2 horas, luego, a 80°C durante 4 horas. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr 3–cloro–5–(prop–1–en–2–il)picolinonitrilo como un sólido de color blanco.

Etapa 2: 2–(prop–1–en–2–il)benzo[f][1,7]naftiridin–5–amina.

Una solución de ácido 2–(*ter*–butoxicarbonilamino)fenilbórico (1,0 eq.) y 3–cloro–5–(prop–1–en–2–il)picolinonitrilo (de la etapa 1) (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (2,0 eq.), en tolueno/etanol (2:1, 0,03 M) se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con metanol. Los sólidos insolubles se separaron mediante la filtración, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr 2–(prop–1–en–2–il)benzo[f][1,7]naftiridin–5–amina como un sólido de color blanco. ^{1}H RMN (dmso–d6): δ 9,03 (d, 1H), 8,96 (d, 1H), 8,55 (d, 1H), 7,47– 7,53 (m, 2H), 7,25 (m, 1H), 7,07 (bs, 2H) 5,80 (s, 1H), 5,36 (s, 1H), 2,27 (s, 3H). LRMS [M + H] = 236,2.

Ejemplo 37.

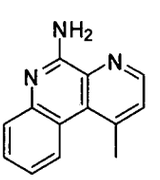
2–Isopropilbenzo[f][1,7]naftiridin–5–amina.



A una solución de 2–(prop–1–en–2–il)benzo[f][1,7]naftiridin–5–amina (Ejemplo 36) en acetato de etilo/metanol (1:4, 0,05 M) se agregó 10% en peso de paladio sobre carbón (0,2 eq.). Se introdujo gas hidrógeno por medio de un balón, y la reacción se agitó durante 3 horas. La mezcla se filtró a través de una almohadilla de celite, lavando con diclorometano. El filtrado se concentró al vacío, y el producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr 2–isopropilbenzo[f][1,7]naftiridin–5–amina en forma de un sólido de color amarillo. ^{1}H RMN ($CDCl_3$): δ 8,69 (d, 1H), 8,49 (d, 1H), 8,25 (dd, 1H), 7,65 (dd, 1H), 7,53 (m, 1H), 7,31 (m, 1H), 6,02 (bs, 2H), 3,15 (septete, 1H), 1,37 (d, 6H). LRMS [M + H] = 238,2.

Ejemplo 38.

1–Metilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 5–bromo–2–cloro–4–metilpiridina 1–óxido.

Una solución de 5–bromo–2–cloro–4–metilpiridina (1,0 eq.) y ácido meta–cloroperbenzoico (mCPBA) (2,5 eq.) en cloroformo (0,1 M) se agitó a 50°C durante la noche. Después de enfriar hasta temperatura ambiente, se agregó $Ca(OH)_2$ (2,5 eq.) a la mezcla de reacción. El precipitado se filtró y se lavó con 5%

de metanol en diclorometano y acetato de etilo. El filtrado se lavó con solución acuosa saturada de $Na_2S_2O_3$ y solución acuosa saturada de $NaHCO_3$. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío hasta obtener un sólido pálido, que se llevó a la siguiente etapa sin otra purificación.

Etapa 2: 3–bromo–6–cloro–4–metilpicolinonitrilo.

A una solución de 5–bromo–2–cloro–4–metilpiridina 1–óxido (de la etapa 1) (1,0 eq.) en acetonitrilo (0,2 M) se agregaron TMSCN (4,0 eq.) y trietilamina (3,0 eq.). La reacción se calentó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, el solvente se concentró al vacío, y el residuo se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–50% de acetato de etilo en hexano, a fin de lograr 3–bromo–6–cloro–4–metilpicolinonitrilo.

Etapa 3: 3–cloro–1–metilbenzo[f][1,7]naftiridin–5–amina.

Una solución de ácido 2–(*ter*–butoxicarbonilamino)fenilbórico (1,0 eq.) y 3–bromo–6–cloro–4–metilpicolinonitrilo (de la etapa 2) (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (2,0 eq.), en tolueno/etanol (2:1, 0,03 M), se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con metanol. Los sólidos insolubles se separaron mediante la filtración, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr 3–cloro–1–metilbenzo[f][1,7]naftiridin–5–amina como un sólido de color blanco. ^{1}H RMN (dmso–d6): δ 8,44 (d, 1H), 7,83 (s, 1H), 7,50– 7,58 (m, 2H), 7,02 (bs, 2H), 2,98 (s, 3H). LRMS [M + H] = 244,1.

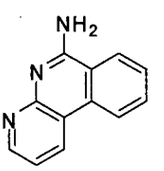
Etapa 4: 1–metilbenzo[f][1,7]naftiridin–5–amina.

A una solución de 3–cloro–1–metilbenzo[f][1,7]naftiridin–5–amina (de la

etapa 3) en acetato de etilo/metanol (1:2, 0,03 M) se agregó 10% en peso de paladio sobre carbón (0,2 eq.). El recipiente de reacción se sacudió en un aparato Parr de hidrógeno bajo 0,34 MPa (50 psi) de hidrógeno, durante la noche. La mezcla se filtró a través de una almohadilla de celite, lavando con diclorometano. El filtrado se concentró al vacío y se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr 1–metilbenzo[f][1,7]naftiridin–5–amina como un sólido de color blanco. ^{1}H RMN ($CDCl_3$): δ 8,63 (d, 1H), 8,44 (d, 1H), 7,71 (dd, 1H), 7,54 (m, 1H), 7,45 (d, 1H), 7,30 (m, 1H), 6,20 (bs, 2H), 3,01 (s, 3H). LRMS [M + H] = 210,1.

Ejemplo 39.

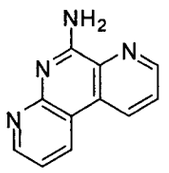
Benzo[c][1,8]naftiridin–6–amina.



Una solución de ter–butil 3–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)piridin–2–ilcarbamato (1,0 eq.) y 2–bromobenzonitrilo (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (2,0 eq.), en tolueno/etanol (2:1, 0,03 M), se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con metanol. Los sólidos insolubles se separaron mediante la filtración, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr benzo[c][1,8]naftiridin–6–amina como un sólido de color blanco. ^{1}H RMN (metanol–d4): δ 8,88 (dd, 1H), 8,67–8,63 (m, 2H), 8,30 (d, 1H), 7,90 (dt, 1H), 7,74 (dt, 1H), 7,36 (dd, 1H). LRMS [M + H] = 196,1.

Ejemplo 40.

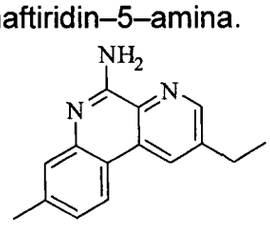
Pirido[3,2–f][1,7]naftiridin–6–amina.



Una solución de ter–butil 3–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)piridin–2–ilcarbamato (1,0 eq.) y 3–bromopicolinonitrilo (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5 % en moles) y solución acuosa de carbonato de sodio, 2 N (2,0 eq.) en tolueno/etanol (2:1, 0,03 M), se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con metanol. Los sólidos insolubles se separaron mediante la filtración, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr pirido[3,2–f][1,7]naftiridin–6–amina como un sólido de color blanco. ^{1}H RMN (dmso–d6): δ 9,14 (dd, 1H), 8,98 (dd, 1H), 8,90 (dd, 1H), 7,93 (dd, 1H), 7,60 (bs, 2H), 7,30 (dd, 1H). LRMS [M + H] = 197.

Ejemplo 41.

2–Etil–8–metilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 8–metil–2–vinilbenzo[f][1,7]naftiridin–5–amina.

Una solución de ter–butil 5–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (del Ejemplo 5/etapa 2) (1,0 eq.) y 3–cloro–5–vinilpicolinonitrilo (del Ejemplo 29/Etapa 1) (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (2,0

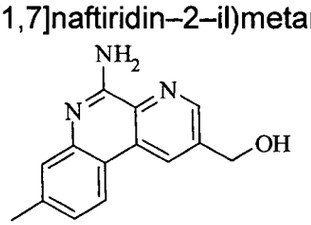
eq.), en tolueno/etanol (2:1, 0,03 M), se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con metanol. Los sólidos insolubles se separaron mediante la filtración, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr 8–metil–2–vinilbenzo[f][1,7]naftiridin–5–amina en forma de un sólido de color amarillo.

Etapa 2: 2–etil–8–metilbenzo[f][1,7]naftiridin–5–amina.

A una solución de 8–metil–2–vinilbenzo[f][1,7]naftiridin–5–amina (de la etapa anterior) en acetato de etilo/metanol (1:4, 0,05 M) se agregó 10% en peso de paladio sobre carbón (0,2 eq.). Se introdujo gas hidrógeno por medio de un balón, y la reacción se agitó durante 3 horas. La mezcla se filtró a través de una almohadilla de celite y se lavó con diclorometano. El filtrado se concentró al vacío y se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr 2–etil–8–metilbenzo[f][1,7]naftiridin–5–amina en forma de un sólido blanquecino. ^{1}H RMN ($CDCl_3$): δ 8,61 (d, 1H), 8,42 (d, 1H), 8,10 (d, 1H), 7,44 (s, 1H), 7,12 (dd, 1H), 6,00 (bs, 2H), 2,84 (q, 2H), 2,45 (s, 3H), 1,33 (t, 3H). LRMS [M + H] = 238,1.

Ejemplo 42.

(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)metanol.



Etapa 1: etil 5–cloro–6–cianonicotinato.

Una solución de etil 5,6–dicloronicotinato (1 eq), cianuro de zinc (0,75 eq.) y tetraquis(trifenil–fosfina)paladio (0,10 eq.) en DMF (0,3 M) se desgaseó y luego se calentó a 100°C durante 3 horas. Se eliminó el solvente al vacío, de modo de

obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr etil 5–cloro–6–cianonicotinato como un sólido de color blanco.

Etapa 2: etil 5–amino–8–metilbenzo[f][1,7]naftiridina–2–carboxilato.

Una solución de ter–butil 5–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (del Ejemplo 5/etapa 2) (1,0 eq.) y etil 5–cloro–6–cianonicotinato (de la etapa anterior) (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (2,0 eq.), en tolueno/etanol (2:1, 0,03 M) se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con metanol. Los sólidos insolubles se separaron mediante la filtración, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr etil 5–amino–8–metilbenzo[f][1,7]naftiridina–2–carboxilato.

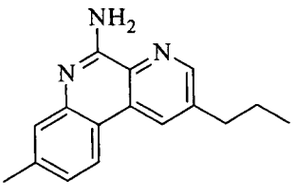
Etapa 3: 2–etil–8–metilbenzo[f][1,7]naftiridin–5–amina.

A una solución agitada de etil 5–amino–8–metilbenzo[f][1,7]naftiridina–2–carboxilato (de la etapa anterior) en THF (0,2 M) enfriada en un baño de hielo–agua se agregó una solución, 1 N, de superhidruro en THF (10 eq.). Al terminar la reacción, la reacción se apagó con HCl, 1 N, y se extrajo con EtOAc. Los extractos orgánicos combinados se concentraron al vacío de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr (5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)metanol como un sólido de color blanco. ^{1}H RMN ($CDCl_3$): δ 8,68 (d, 1H), 8,52 (d, 1H), 8,04 (d, 1H), 7,44 (s, 1H), 7,12 (dd, 1H), 6,00 (bs, 2H), 4,90 (s, 2H), 2,45

(s, 3H). LRMS [M + H] = 240,1.

Ejemplo 43.

8–Metil–2–propilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: (E)–3–cloro–5–(prop–1–enil)picolinonitrilo.

Una solución de 3,5–dicloropicolinonitrilo (1,0 eq.), (E)–4,4,5,5–tetrametil–2–(prop–1–enil)–1,3,2–dioxaborolano (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5 % en moles) y solución acuosa de carbonato de sodio, 2 N (3,4 eq.), en tolueno/etanol (2:1, 0,04 M), se agitó a 95°C durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr un sólido de color blanco de (E)–3–cloro–5–(prop–1–enil)picolinonitrilo.

Etapa 2: (E)–8–metil–2–(prop–1–enil)benzo[f][1,7]naftiridin–5–amina.

Una solución de ter–butil 5–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (del Ejemplo 5/Etapa 2) (1,0 eq.) y (E)–3–cloro–5–(prop–1–enil)picolinonitrilo (de la etapa previa) (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (2,0 eq.), en tolueno/etanol (2:1, 0,03 M), se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, el contenido de la reacción se diluyó con metanol. Los sólidos insolubles se separaron mediante la filtración, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El material bruto se

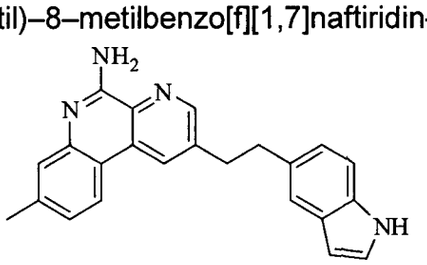
purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr (E)–8–metil–2–(prop–1–enil)benzo[f][1,7]naftiridin–5–amina en forma de un sólido de color amarillo.

Etapa 3: 8–metil–2–propilbenzo[f][1,7]naftiridin–5–amina.

A una solución de (E)–8–metil–2–(prop–1–enil)benzo[f][1,7]naftiridin–5–amina (de la etapa previa) en acetato de etilo/metanol (1:4, 0,05 M) se agregó 10% en peso de paladio sobre carbón (0,2 eq.). Se introdujo gas hidrógeno por medio de un balón, y la reacción se agitó durante 3 horas. La mezcla se filtró a través de una almohadilla de celite, lavando con diclorometano. El filtrado se concentró al vacío y se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr 8–metil–2–propilbenzo[f][1,7]naftiridin–5–amina en forma de un sólido blanquecino. ^{1}H RMN ($CDCl_3$): δ 8,59 (d, 1H), 8,41 (d, 1H), 8,10 (d, 1H), 7,43 (s, 1H), 7,13 (dd, 1H), 5,94 (bs, 2H), 2,78 (t, 2H), 2,44 (s, 3H), 1,75 (m, 2H), 0,95 (t, 3H). LRMS [M + H] = 252,1.

Ejemplo 44.

2–(2–(1H–Indol–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 5–((trietilsilil)etinil)–1H–indol.

A un vial de centelleo se agregaron –yodo–1H–indol (1,1 eq.), trietil(etinil)silano (1 eq.), trietilamina (5 eq.) y DMF anhidra (0,2 M). El vial se sometió al vacío y se inundó con nitrógeno tres veces. Se agregaron CuI (0,1 eq.) y bis(trifenilfosfina)dicloro–paladio(II) (0,1 eq.). El vial se selló y se calentó a 60°C durante la noche. Al terminar la reacción según el control de TLC, el contenido del

vial se cargó en una columna de gel de sílice pretratada con hexanos. La columna se lavó con hexanos y dietil éter hasta recoger todos los eluyentes que contenían producto. La cuidadosa destilación de los hexanos y el éter usando un evaporador giratorio con mínimo calentamiento logró el producto 5–((trietilsilil)etinil)–1H–indol en forma de un aceite incoloro, que se llevó directamente a la siguiente etapa.

Etapa 2: 5–etinil–1H–indol.

Una solución agitada de 5–((trietilsilil)etinil)–1H–indol (de la etapa previa) en THF (0,2 M), enfriada a 0°C, se trató con una solución (0,5 eq.) de fluoruro de tetrabutilamonio, por goteo. La mezcla de reacción se tornó negra, y continuó en agitación durante 30 minutos antes de entibiar hasta t. a. TLC mostró la conversión completa. La reacción se apagó con agua y se extrajo con dietil éter. Las capas orgánicas combinadas se secaron sobre Na_2SO_4 anhidro y se concentraron usando un evaporador giratorio con mínimo calentamiento. La cromatografía (gel de sílice, dietil éter) logró el producto 5–etinil–1H–indol en forma de un aceite incoloro.

Etapa 3: 5–((1H–indol–5–il)etinil)–3–cloropicolinonitrilo.

A un matraz de base redonda cubierto con un tabique se agregaron 5–etinil–1H–indol (de la etapa previa) (1,1 eq), 3,5–dicloropicolinonitrilo (1 eq.), trietilamina (5 eq.) y DMF anhidra (0,2 M). El matraz se sometió al vacío y se inundó con nitrógeno tres veces. Se agregaron CuI (0,05 eq.) y bis(trifenilfosfina)dicloro–paladio (II) (0,05 eq). El tabique se reemplazó con un condensador de reflujo, y el matraz se calentó a 60°C durante la noche en una atmósfera de nitrógeno. Al terminar la reacción según el control de TLC, el contenido del matraz se cargó en una columna de gel de sílice grande pretratada con hexanos. La cromatografía instantánea (gel de sílice, hexanos:EtOAc (1:4%)) logró el producto 5–((1H–indol–5–il)etinil)–3–cloropicolinonitrilo.

Etapa 4: 2–((1H–indol–5–il)etinil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

A un matraz de base redonda con un condensador de reflujo se agregaron 5–((1H–indol–5–il)etinil)–3–cloropicolinonitrilo (de la etapa previa) (1 eq.), ter–butil 2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (del Ejemplo 5/Etapa 2) (1,25 eq.), K_3PO_4 (2 eq.), tris(dibencilidenoacetona)dipaladio (0) (0,05 eq.) y 2–diciclohexilfosfino–2',6'–dimetoxibifenilo (0,1 eq.). Se agregaron n–butanol y agua (5:2, 0,2 M), y se desgaseó el contenido (vacío, seguido de inundación de nitrógeno) tres veces. La mezcla de reacción se agitó vigorosamente en nitrógeno a 100°C durante la noche, en un baño de aceite. Se enfrió el contenido y se recogió en 200 ml de agua, y luego se extrajo con cloruro de metileno. Las capas orgánicas combinadas se secaron (Na_2SO_4) y se concentraron. La cromatografía instantánea (gel de sílice, 0–50% de EtOAc en CH_2Cl_2) logró el producto 2–((1H–indol–5–il)etinil)–8–metilbenzo[f][1,7]naftiridin–5–amina en forma de un sólido de color amarillo.

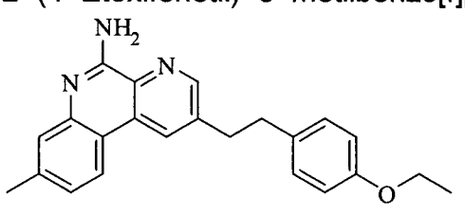
Etapa 5: 2–(2–(2,3–dihidrobenzofuran–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

A un matraz de base redonda se agregó 2–((1H–indol–5–il)etinil)–8–metilbenzo[f][1,7]naftiridin–5–amina (de la etapa previa) (1 eq.) con una barra agitadora. Se agregaron etanol y cloruro de metileno (1:2, 0,2 M), seguidos de paladio sobre carbón (polvo activado, húmedo, 10% sobre carbón, 0,1 eq.). El contenido se sometió al vacío, y luego se inundó con nitrógeno tres veces. La mezcla de reacción se agitó vigorosamente en un balón de hidrógeno a temperatura ambiente durante la noche. A continuación, la mezcla de reacción se filtró a través de una almohadilla de celite, y la almohadilla de celite se lavó subsiguientemente con cloruro de metileno y EtOAc, hasta que el filtrado no tuvo absorción de UV. Los lavados orgánicos combinados se concentraron. La cromatografía instantánea (gel de sílice, 0–50% de EtOAc en CH_2Cl_2) logró el

producto 2–(2–(2,3–Dihidrobenzofuran–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina en forma de un sólido de color amarillo. ^{1}H RMN ($CDCl_3$): δ 8,54 (d, 1H), 8,34 (d, 1H), 8,28 (s, 1H), 7,99 (d, 1H), 7,64 – 7,56 (m, 1H), 7,50 – 7,35 (m, 1H), 7,24 (d, 1H), 7,12 (t, 1H), 7,08 (dd, 1H), 6,92 (dd, 1H), 6,41 (s, 1H), 6,01 (bs, 2H), 3,16 – 3,12 (m, 2H), 3,10 – 3,05 (m, 2H), 2,43 (s, 3H). LRMS [M + H] = 353,2.

Ejemplo 45.

2–(4–Etoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 3–cloro–5–((4–etoxifenil)etinil)picolinonitrilo.

A un matraz de base redonda cubierto con un tabique se agregaron 1–etoxi–4–etinilbenceno (1,1 eq), 3,5–dicloropicolinonitrilo (1 eq.), trietilamina (5 eq.) y DMF anhidra (0,2 M). El matraz se sometió al vacío y se inundó con nitrógeno tres veces. Se agregaron CuI (0,05 eq.) y bis(trifenilfosfina)dicloro–paladio (II) (0,05 eq). El tabique se reemplazó con un condensador de reflujo, y el matraz se calentó a 60°C durante la noche en una atmósfera de nitrógeno. Al terminar la reacción según el control de TLC, el contenido del matraz se cargó en una columna de gel de sílice grande pretratada con hexanos. La cromatografía instantánea (gel de sílice, hexanos:EtOAc (1:4%)) logró el producto 3–cloro–5–((4–etoxifenil)etinil)picolinonitrilo.

Etapa 2: 2–((4–etoxifenil)etinil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

A un matraz de base redonda con condensador de reflujo se agregaron 3–cloro–5–((4–etoxifenil)etinil)picolinonitrilo (de la etapa previa) (1 eq.), ter–butil 5–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (del Ejemplo 5/Etapa 2) (1,25 eq.), K_3PO_4 (2 eq.), tris(dibencilidenoacetona)dipaladio (0) (0,05 eq.), y 2–diciclohexilfosfino–2',6'–dimetoxibifenilo (0,1 eq.). Se agregaron n–

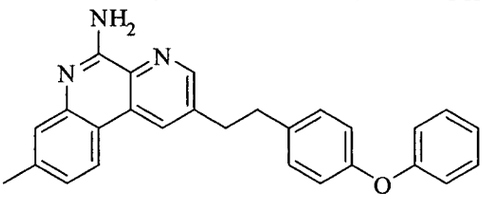
butanol y agua (5:2, 0,2 M), y el contenido se desgaseó (vacío, seguido de inundación de nitrógeno) tres veces. La mezcla de reacción se agitó vigorosamente en nitrógeno a 100°C durante la noche, en un baño de aceite. El contenido se enfrió y se recogió en 200 ml de agua, y luego se extrajo con cloruro de metileno. Las capas orgánicas combinadas se secaron (Na_2SO_4) y se concentraron. La cromatografía instantánea (gel de sílice, 0–50% de EtOAc en CH_2Cl_2) logró el producto 2–((4–etoxifenil)etinil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

Etapa 3: 2–(4–etoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

A un matraz de base redonda se agregó 2–((4–etoxifenil)etinil)–8–metilbenzo[f][1,7]naftiridin–5–amina (de la etapa previa) (1 eq.) con una barra agitadora. Se agregaron etanol y cloruro de metileno (1:2, 0,2 M), seguidos de paladio sobre carbón (polvo activado, húmedo, 10% en carbón, 0,1 eq.). Los contenidos se desgasearon al vacío seguido de la inundación de hidrógeno (tres veces). La mezcla de reacción se agitó vigorosamente en un balón de hidrógeno a temperatura ambiente durante la noche. A continuación, la mezcla de reacción se filtró a través de una almohadilla de celite, y la almohadilla de celite se lavó subsiguientemente con cloruro de metileno y EtOAc, hasta que el filtrado no tuvo absorción de UV. Los lavados orgánicos combinados se concentraron. La cromatografía instantánea (gel de sílice, 0–50% de EtOAc en CH_2Cl_2) logró el producto en forma de un sólido de color amarillo. La recristalización adicional usando tolueno logró el producto 2–(4–etoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina en forma de un cristal fino de color blanco. ^1H RMN ($CDCl_3$): δ 8,52 (d, 1H), 8,30 (d, 1H), 8,10 (d, 1H), 7,46 (s, 1H), 7,12 (dd, 1H), 7,06 (d, 2H), 6,75 (d, 2H), 5,95 (bs, 2H), 3,93 (q, 2H), 3,11 – 3,05 (dd, 2H), 2,95 – 2,90 (dd, 2H), 2,44 (s, 3H), 1,33 (t, 3H). LRMS [M + H] = 358,2.

Ejemplo 46.

8–Metil–2–(4–fenoxifenetil)benzo[f][1,7]naftiridin–5–amina.



Etapa 1: 3–cloro–5–((4–fenoxifenil)etinil)picolinonitrilo.

Se preparó 3–cloro–5–((4–fenoxifenil)etinil)picolinonitrilo a partir de 1–etinil–4–fenoxibenceno (comercial), siguiendo los procedimientos descriptos para el Ejemplo 45, Etapa 1.

Etapa 2: 8–metil–2–((4–fenoxifenil)etinil)benzo[f][1,7]naftiridin–5–amina.

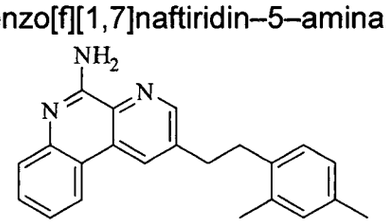
Se preparó 8–metil–2–((4–fenoxifenil)etinil)benzo[f][1,7]naftiridin–5–amina a partir de 3–cloro–5–((4–fenoxifenil)etinil)picolinonitrilo (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 45, etapa 2.

Etapa 3: 8–metil–2–(4–fenoxifenetil)benzo[f][1,7]naftiridin–5–amina.

Se preparó 8–metil–2–(4–fenoxifenetil)benzo[f][1,7]naftiridin–5–amina a partir de 8–metil–2–((4–fenoxifenil)etinil)benzo[f][1,7]naftiridin–5–amina (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 45, etapa 3. ^{1}H RMN ($CDCl_3$): δ 8,54 (d, 1H), 8,30 (d, 1H), 8,01 (d, 1H), 7,45 (s, 1H), 7,25 – 7,20 (m, 2H), 7,12 (dd, 1H), 7,07 – 6,84 (m, 8H), 6,00 (bs, 2H), 3,13 – 3,08 (dd, 2H), 2,99 – 2,94 (dd, 2H), 2,44 (s, 3H). LRMS [M + H] = 406,2.

Ejemplo 47.

2–(2,4–Dimetilfenetil)benzo[f][1,7]naftiridin–5–amina.



Etapa 1: ((2,4–dimetilfenil)etinil)trietilsilano.

Se preparó ((2,4–dimetilfenil)etinil)trietilsilano a partir de 1–yodo–2,4–

dimetilbenceno (comercial), siguiendo los procedimientos descriptos para el Ejemplo 44, etapa 1.

Etapa 2: 1–etinil–2,4–dimetilbenceno.

Se preparó 1–etinil–2,4–dimetilbenceno a partir de ((2,4–dimetilfenil)etinil)trietilsilano (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 44, etapa 2,

Etapa 3: 3–cloro–5–((2,4–dimetilfenil)etinil)picolinonitrilo.

Se preparó 3–cloro–5–((2,4–dimetilfenil)etinil)picolinonitrilo a partir de 1–etinil–2,4–dimetilbenceno (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 44, etapa 3,

Etapa 4: 2–((2,4–dimetilfenil)etinil)benzo[f][1,7]naftiridin–5–amina.

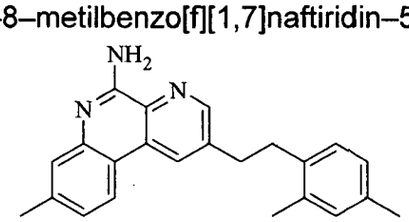
Se preparó 2–((2,4–dimetilfenil)etinil)benzo[f][1,7]naftiridin–5–amina a partir de 3–cloro–5–((2,4–dimetilfenil)etinil)–picolinonitrilo (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 44, etapa 4.

Etapa 5: 2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina.

Se preparó 2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina a partir de 2–((2,4–dimetilfenil)etinil)benzo[f][1,7]naftiridin–5–amina (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 44, etapa 5. ^{1}H RMN ($CDCl_3$): δ 8,60 (d, 1H), 8,33 (d, 1H), 8,14 (d, 1H), 7,67 (d, 1H), 7,54 (t, 1H), 7,31 (t, 1H), 6,96 – 6,86 (m, 3H), 6,29 (bs, 2H), 3,04 – 3,10 (dd, 2H), 2,97 – 2,91 (dd, 2H), 2,24 (s, 3H), 2,20 (s, 3H). LRMS [M + H] = 328,2.

Ejemplo 48.

2–(2,4–Dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 2–((2,4–dimetilfenil)etinil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

Se preparó 2–((2,4–dimetilfenil)etinil)–8–metilbenzo[f][1,7]naftiridin–5–

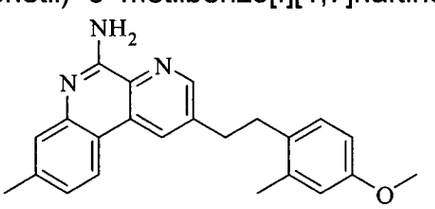
amina a partir de 3–cloro–5–((2,4–dimetilfenil)etinil)picolinonitrilo (del Ejemplo 47/Etapa 3) y ter–butil 5–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (del Ejemplo 5/Etapa 2), siguiendo los procedimientos descriptos para el Ejemplo 44, etapa 4.

Etapa 2: 2–(2,4–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

Se preparó 2–(2,4–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina a partir de 1–etinil–4–fenoxibenceno (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 44, etapa 5. ^{1}H RMN ($CDCl_3$): δ 8,56 (d, 1H), 8,28 (d, 1H), 8,00 (d, 1H), 7,46 (s, 1H), 7,14 (dd, 1H), 6,95 – 6,85 (m, 3H), 6,26 (bs, 2H), 3,08 – 3,02 (dd, 2H), 2,96 – 2,90 (dd, 2H), 2,45 (s, 3H), 2,23 (s, 3H), 2,19 (s, 3H). LRMS [M + H] = 342,2.

Ejemplo 49.

2–(4–Metoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 3–cloro–5–((4–metoxi–2–metilfenil)etinil)picolinonitrilo.

Se preparó 3–cloro–5–((4–metoxi–2–metilfenil)etinil)picolinonitrilo a partir de 1–etinil–4–metoxi–2–metilbenceno (comercial), siguiendo el procedimiento descripto para el Ejemplo 44/Etapa 3.

Etapa 2: 2–((4–metoxi–2–metilfenil)etinil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

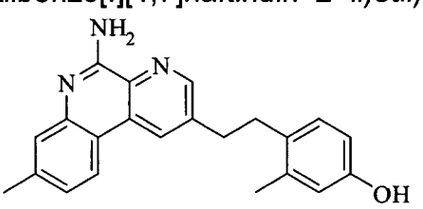
Se preparó 2–((4–metoxi–2–metilfenil)etinil)–8–metilbenzo[f][1,7]naftiridin–5–amina a partir de 3–cloro–5–(4–metoxi–2–metilfenetil)picolinonitrilo (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 44, etapa 4.

Etapa 3: 2–(4–metoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

Se preparó 2–(4–metoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina a partir de 2–((4–metoxi–2–metilfenil)etinil)–8–metilbenzo[f][1,7]naftiridin–5–amina (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 44, etapa 5. ^{1}H RMN ($CDCl_3$): δ 8,53 (d, 1H), 8,29 (d, 1H), 8,01 (d, 1H), 7,44 (s, 1H), 7,12 (dd, 1H), 6,93 (d, 1H), 6,67 (d, 1H), 6,60 (dd, 1H), 5,93 (bs, 2H), 3,70 (s, 3H), 3,05 – 3,00 (dd, 2H), 2,93 – 2,88 (dd, 2H), 2,44 (s, 3H), 2,19 (s, 3H). LRMS [M + H] = 358,2.

Ejemplo 50.

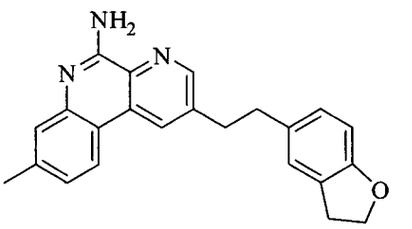
4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol.



A una solución agitada de 2–(4–metoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina (Ejemplo 49) en cloruro de metileno (0,2 M) en un baño de hielo–agua se agregó una solución, 1 N, de BBr_3 (2 eq.) en CH_2Cl_2, por goteo. En un período de 30 minutos, la reacción se apagó con metanol y se concentró al vacío, de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–20% de metanol en diclorometano, a fin de lograr 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol como un sólido de color blanco. ^{1}H RMN (DMSO–d_6): δ 8,99 (s, 1H), 8,75 (d, 1H), 8,60 (d, 1H), 8,27 (d, 1H), 7,28 (s, 1H), 7,09 (dd, 1H), 6,99 (bs, 2H), 6,88 (d, 1H), 6,49 (d, 1H), 6,42 (dd, 1H), 3,02 – 2,96 (dd, 2H), 2,86 – 2,81 (dd, 2H), 2,38 (s, 3H), 2,13 (s, 3H). LRMS [M + H] = 344,2.

Ejemplo 51.

2–(2–(2,3–Dihidrobenzofuran–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: ((2,3–dihidrobenzofuran–5–il)etinil)trietilsilano.

Se preparó ((2,3–dihidrobenzofuran–5–il)etinil)trietilsilano a partir de 5–yodo–2,3–dihidrobenzofurano (comercial), siguiendo los procedimientos descriptos para el Ejemplo 44, etapa 1.

Etapa 2: 5–etinil–2,3–dihidrobenzofurano.

Se preparó 5–etinil–2,3–dihidrobenzofurano a partir de ((2,3–dihidrobenzofuran–5–il)etinil)trietilsilano (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 2.

Etapa 3: 3–cloro–5–((2,3–dihidrobenzofuran–5–il)etinil)picolinonitrilo.

Se preparó 3–cloro–5–((2,3–dihidrobenzofuran–5–il)etinil)picolinonitrilo a partir de 5–etinil–2,3–dihidrobenzofurano (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 3.

Etapa 4: 2–((2,3–dihidrobenzofuran–5–il)etinil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

Se preparó 2–((2,3–dihidrobenzofuran–5–il)etinil)–8–metilbenzo[f][1,7]naftiridin–5–amina a partir de 3–cloro–5–(4–metoxi–2–metilfenetil)picolinonitrilo (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 4.

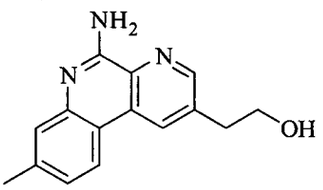
Etapa 5: 2–(2–(2,3–dihidrobenzofuran–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

Se preparó 2–(2–(2,3–dihidrobenzofuran–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina a partir de 2–((2,3–dihidrobenzofuran–5–il)etinil)–8–metilbenzo[f][1,7]naftiridin–5–amina (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 5. ^{1}H RMN ($CDCl_3$): δ 8,62 (d,

1H), 8,40 (d, 1H), 8,11 (d, 1H), 7,53 (s, 1H), 7,21 (dd, 1H), 6,99 (s, 1H), 6,95 (dd, 1H), 6,74 (d, 1H), 6,05 (bs, 2H), 4,57 (t, 2H), 3,19 – 3,13 (m, 4H), 3,03 – 2,98 (dd, 2H), 2,54 (s, 3H). LRMS [M + H] = 356,2.

Ejemplo 52.

2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etanol.



Etapa 1: (Z)–3–cloro–5–(2–etoxivinil)picolinonitrilo.

Se preparó (Z)–3–cloro–5–(2–etoxivinil)picolinonitrilo a partir de (Z)–2–(2–etoxivinil)–4,4,5,5–tetrametil–1,3,2–dioxaborolano (comercial), siguiendo los procedimientos descriptos para el Ejemplo 43/Etapa 1.

Etapa 2: (Z)–2–(2–etoxivinil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

Se preparó (Z)–2–(2–etoxivinil)–8–metilbenzo[f][1,7]naftiridin–5–amina a partir de (Z)–3–cloro–5–(2–etoxivinil)picolinonitrilo (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 43/Etapa 2.

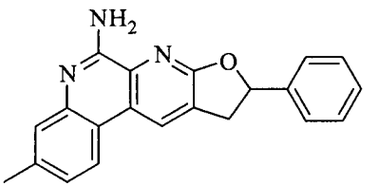
Etapa 3: 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etanol.

Una solución de (Z)–2–(2–etoxivinil)–8–metilbenzo[f][1,7]naftiridin–5–amina (de la etapa previa) en una mezcla de 2:5 de HCl conc. y dioxano (0,1 M) se calentó a 60°C durante la noche. Al enfriar a temperatura ambiente, la mezcla de reacción se trató con un exceso de solución saturada de $NaHCO_3$, y luego, se extrajo con EtOAc. Los extractos orgánicos combinados se concentraron y se recogieron en THF (0,2 M), y luego se trataron con solución de superhidruro, 1 N, en THF (10 eq.) a 0°C. La mezcla de reacción se dejó entibiar hasta temperatura ambiente y se agitó durante la noche. La reacción se trabajó siguiendo los procedimientos descriptos para el Ejemplo 42/Etapa 3, a fin de lograr 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etanol en forma de un sólido de color blanco. ^1H RMN ($CDCl_3$): δ 8,61 (d, 1H), 8,47 (d, 1H), 8,01 (d, 1H), 7,41 (s, 1H),

7,10 (d, 1H), 6,40 (s, 1H), 6,01 (bs, 2H), 4,01 (t, 2H), 3,06 (t, 2H), 2,43 (s, 3H). LRMS [M + H] = 254,1.

Ejemplo 53.

3–Metil–9–fenil–9,10–dihidrobenzo[f]furo[2,3–b][1,7]naftiridin–6–amina.



Etapa 1: 5–bromo–2–cloro–3–metilpiridina 1–óxido.

Se preparó 5–bromo–2–cloro–3–metilpiridina 1–óxido a partir de 5–bromo–2–cloro–3–metilpiridina (comercial), siguiendo los procedimientos descriptos para el Ejemplo 19/Etapa 1.

Etapa 2: 3–bromo–6–cloro–5–metilpicolinonitrilo.

Se preparó 3–bromo–6–cloro–5–metilpicolinonitrilo a partir de (Z)–3–cloro–5–(2–etoxivinil)picolinonitrilo (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 19/Etapa 2.

Etapa 3: 3–bromo–6–cloro–5–(2–hidroxi–2–feniletil)picolinonitrilo.

Una solución de 3–bromo–6–cloro–5–metilpicolinonitrilo (de la etapa previa) en THF (0,2 M) se enfrió hasta –78°C. Se agregó LDA (solución 2 N, 2 eq.) por goteo. La reacción se mantuvo en agitación a –78°C durante 1 hora, y luego se le añadió benzaldehído (1 eq.). La reacción se mantuvo en agitación a –78°C durante otros 30 minutos, antes de permitir entibiar lentamente hasta temperatura ambiente. La reacción se apagó con NH_4Cl saturado y se extrajo con EtOAc. Los lavados orgánicos combinados se concentraron. La cromatografía instantánea (gel de sílice, 20–50% de EtOAc en hexanos) logró el producto 3–bromo–6–cloro–5–(2–hidroxi–2–feniletil)picolinonitrilo en forma de un sólido de color amarillo.

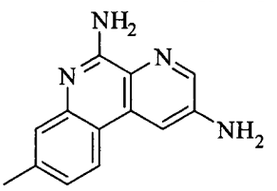
Etapa 4: 3–metil–9–fenil–9,10–dihidrobenzo[f]furo[2,3–b][1,7]naftiridin–6–amina.

Se preparó 3–metil–9–fenil–9,10–dihidrobenzo[f]furo[2,3–b][1,7]naftiridin–

6–amina a partir de 3–bromo–6–cloro–5–metilpicolinonitrilo (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 4. ^{1}H RMN ($CDCl_3$): δ 8,45 (s, 1H), 7,98 (d, 1H), 7,45 (s, 1H), 7,40 – 7,28 (m, 5H), 7,12 (d, 1H), 5,93 (t, 1H), 5,93 (brs, 2H), 3,86 (dd, 1H), 3,40 (dd, 1H), 2,44 (s, 3H). LRMS [M + H] = 328,1.

Ejemplo 54.

8–Metilbenzo[f][1,7]naftiridina–2,5–diamina.



Etapa 1: ter–butil 5,6–dicloropiridin–3–ilcarbamato.

A una solución de 5,6–dicloropiridin–3–amina (comercial) en THF (0,2 M) agitada a 0°C se agregó $(BOC)_2O$ (1,2 eq.). La mezcla de reacción se calentó a 40°C hasta la conversión completa según el control de TLC. La mezcla de reacción entonces se concentró. La cromatografía instantánea (gel de sílice, 20–50% de EtOAc en hexanos) del producto bruto logró ter–butil 5,6–dicloropiridin–3–ilcarbamato.

Etapa 2: ter–butil 5–cloro–6–cianopiridin–3–ilcarbamato.

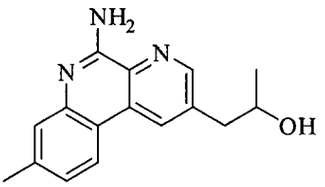
Se preparó ter–butil 5–cloro–6–cianopiridin–3–ilcarbamato a partir de ter–butil 5,6–dicloropiridin–3–ilcarbamato (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 42/Etapa 1.

Etapa 3: 8–metilbenzo[f][1,7]naftiridina–2,5–diamina.

Se preparó 8–metilbenzo[f][1,7]naftiridina–2,5–diamina (como producto menor) junto con ter–butil 5–amino–8–metilbenzo[f][1,7]naftiridin–2–ilcarbamato (como producto mayor) a partir de ter–butil 5–cloro–6–cianopiridin–3–ilcarbamato (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 5/Etapa 2. ^{1}H RMN (DMSO–d_6): δ 10,11 (s, 1H), 9,02 (s, 1H), 8,82 (d, 1H), 8,06 (d, 1H), 7,34 (s, 1H), 7,15 (dd, 1H), 6,99 (s, 2H), 2,44 (s, 3H). LRMS [M + H] = 225,1.

Ejemplo 55.

1–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)propan–2–ol.



Etapa 1: 3–bromo–5–metilpicolinonitrilo.

Se preparó 3–bromo–5–metilpicolinonitrilo a partir de 2,3–dibromo–5–metilpiridina (comercial), siguiendo los procedimientos descriptos para el Ejemplo 42/Etapa 1.

Etapa 2: 3–bromo–5–(2–hidroxipropil)picolinonitrilo.

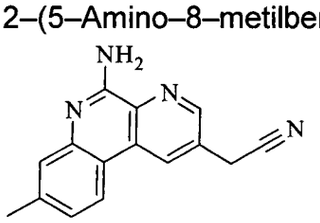
Se preparó 3–bromo–5–(2–hidroxipropil)picolinonitrilo a partir de 3–bromo–5–metilpicolinonitrilo (de la etapa previa) y acetaldehído, siguiendo los procedimientos descriptos para el Ejemplo 53/Etapa 3.

Etapa 3: 1–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)propan–2–ol.

Se preparó 1–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)propan–2–ol a partir de 3–bromo–5–(2–hidroxipropil)picolinonitrilo (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 53, etapa 4. ^{1}H RMN (metanol–d_4): δ 8,72 (d, 1H), 8,68 (d, 1H), 8,24 (d, 1H), 7,38 (s, 1H), 7,18 (dd, 1H), 4,16 – 4,07 (m, 1H), 3,05 – 2,99 (m, 2H), 2,97 – 2,90 (m, 2H), 2,47 (s, 3H), 1,28 (d, 3H). LRMS [M + H] = 268,1.

Ejemplo 56.

2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)acetonitrilo.



Etapa 1: 2,3–dicloro–5–((metoximetoxi)metil)piridina.

A una solución agitada de (5,6–dicloropiridin–3–il)metanol (comercial) en CH_2Cl_2 (0,2 M) a 0°C se agregaron trietilamina (3 eq.) y cloro(metoxi)metano (2

eq.). Después de agitar a 0°C durante 3 horas, la mezcla de reacción se concentró, y el producto bruto se purificó por medio de la cromatografía (gel de sílice, 20–50% de EtOAc en hexanos), a fin de lograr 2,3–dicloro–5–((metoximetoxi)metil)piridina en forma de un aceite incoloro.

Etapa 2: 3–cloro–5–((metoximetoxi)metil)picolinonitrilo.

Se preparó 3–cloro–5–((metoximetoxi)metil)picolinonitrilo a partir de 2,3–dicloro–5–((metoximetoxi)metil)piridina (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 42/Etapa 1.

Etapa 3: 3–cloro–5–(hidroximetil)picolinonitrilo.

A una solución agitada de 2,3–dicloro–5–((metoximetoxi)metil)piridina (de la etapa previa) en metanol (0,2 M) se agregó HCl conc. (10 eq.). Después de agitar a temperatura ambiente durante la noche, la mezcla de reacción se concentró al vacío, y el producto bruto resultante se purificó mediante la cromatografía (gel de sílice, 20–50% de EtOAc en hexanos) a fin de lograr 3–cloro–5–(hidroximetil)picolinonitrilo.

Etapa 4: 3–cloro–5–(clorometil)picolinonitrilo.

A una solución agitada de 3–cloro–5–(hidroximetil)picolinonitrilo (de la etapa previa) en CH_2Cl_2 (0,2 M) a 0°C se agregó cloruro de tionilo (10 eq.). Después de agitar a temperatura ambiente durante la noche, la mezcla de reacción se concentró al vacío, y el producto bruto resultante se purificó por medio de la cromatografía (gel de sílice, 20–50% de EtOAc en hexanos) a fin de lograr 3–cloro–5–(clorometil)picolinonitrilo en forma de un aceite incoloro.

Etapa 5: 3–cloro–5–(cianometil)picolinonitrilo.

A una solución de 3–cloro–5–(clorometil)picolinonitrilo (de la etapa previa) en DMSO (0,2 M) se agregó cianuro de sodio (1,25 eq.). La mezcla de reacción se calentó a 130°C con irradiación de microondas. La mezcla de reacción se recogió en agua y EtOAc, y se extrajo con EtOAc. Las fases orgánicas

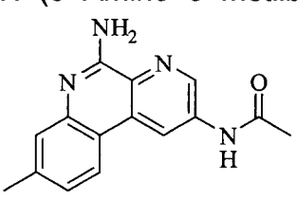
combinadas se secaron sobre Na_2SO_4 anhidro y se concentraron. La cromatografía instantánea (gel de sílice, 20–50% de EtOAc en hexanos) del producto bruto logró 3–cloro–5–(cianometil)picolinonitrilo.

Etapa 6: 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)acetonitrilo.

Se preparó 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)acetonitrilo a partir de 3–cloro–5–(cianometil)picolinonitrilo (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 4. ^{1}H RMN (metanol–d_4): δ 8,79 (d, 1H), 8,78 (d, 1H), 8,20 (d, 1H), 7,66 (s, 2H), 7,36 (s, 1H), 7,18 (dd, 1H), 4,15 (d, 2H), 2,43 (s, 3H). LRMS [M + H] = 249,1.

Ejemplo 57.

N–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)acetamida.



Etapa 1: N–(5,6–dicloropiridin–3–il)acetamida.

A una solución agitada de 5,6–dicloropiridin–3–amina (comercial) y trietil amina (3 eq.) en CH_2Cl_2 (0,2 M) a 0°C se agregó cloruro de acetilo (2 eq.). Después de agitar a temperatura ambiente durante la noche, la mezcla de reacción se concentró al vacío, y el residuo bruto resultante se purificó mediante la cromatografía (gel de sílice, 20–50% de EtOAc en hexanos) a fin de lograr N–(5,6–dicloropiridin–3–il)acetamida.

Etapa 2: N–(5–cloro–6–cianopiridin–3–il)acetamida.

Se preparó N–(5–cloro–6–cianopiridin–3–il)acetamida a partir de N–(5,6–dicloropiridin–3–il)acetamida (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 42/Etapa 1.

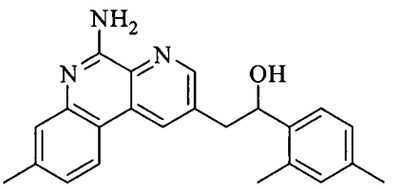
Etapa 3: N–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)acetamida.

Se preparó N–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)acetamida a partir de N–(5–cloro–6–cianopiridin–3–il)acetamida (de la etapa previa), siguiendo

los procedimientos descriptos para el Ejemplo 44/Etapa 4. ^{1}H RMN (DMSO–d_6): δ 10,99 (s, 1H), 8,18 (d, 1H), 8,95 (d, 1H), 8,12 (d, 1H), 7,44 (s, 1H), 7,35 (dd, 1H), 2,43 (s, 3H), 2,16 (s, 3H). LRMS [M + H] = 267,1.

Ejemplo 58.

2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–(2,4–dimetilfenil)etanol.



Etapa 1: 3–bromo–5–(2–(2,4–dimetilfenil)–2–hidroxietil)picolinonitrilo.

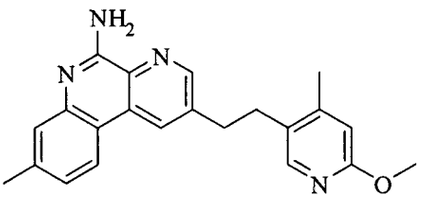
Se preparó 3–bromo–5–(2–(2,4–dimetilfenil)–2–hidroxietil)picolinonitrilo a partir de 3–bromo–5–metilpicolinonitrilo (Ejemplo 55/Etapa 1) y 2,4–dimetilbenzaldehído, siguiendo los procedimientos descriptos para el Ejemplo 53/Etapa 3.

Etapa 2: 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–(2,4–dimetilfenil)etanol.

Se preparó 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–(2,4–dimetilfenil)etanol a partir de 3–bromo–5–(2–(2,4–dimetilfenil)–2–hidroxietil)picolinonitrilo (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 53/Etapa 4. ^{1}H RMN ($CDCl_3$): δ 8,67 (d, 1H), 8,45 (d, 1H), 8,06 (d, 1H), 7,57 (s, 1H), 7,42 (d, 1H), 7,23 (d, 1H), 7,11 (d, 1H), 7,01 (s, 1H), 5,31(dd, 1H), 3,28 – 3,25 (m, 2H), 2,53 (s, 3H), 2,35 (s, 3H), 2,33 (s, 3H). LRMS [M + H] = 358,2.

Ejemplo 59.

2–(2–(6–Metoxi–4–metilpiridin–3–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 2–metoxi–4–metil–5–((trietilsilil)etinil)piridina.

Se preparó 2–metoxi–4–metil–5–((trietilsilil)etinil)piridina a partir de 5–bromo–2–metoxi–4–metilpiridina (comercial), siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 1.

Etapa 2: 5–etinil–2–metoxi–4–metilpiridina.

Se preparó 5–etinil–2–metoxi–4–metilpiridina a partir de 2–metoxi–4–metil–5–((trietilsilil)etinil)piridina (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 2.

Etapa 3: 3–cloro–5–((6–metoxi–4–metilpiridin–3–il)etinil)picolinonitrilo.

Se preparó 3–cloro–5–((6–metoxi–4–metilpiridin–3–il)etinil)picolinonitrilo a partir de 5–etinil–2–metoxi–4–metilpiridina (de la etapa previa) siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 3.

Etapa 4: 2–((6–metoxi–4–metilpiridin–3–il)etinil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

Se preparó 2–((6–metoxi–4–metilpiridin–3–il)etinil)–8–metilbenzo[f][1,7]naftiridin–5–amina a partir de 3–cloro–5–((6–metoxi–4–metilpiridin–3–il)etinil)picolinonitrilo (de la etapa previa) siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 4.

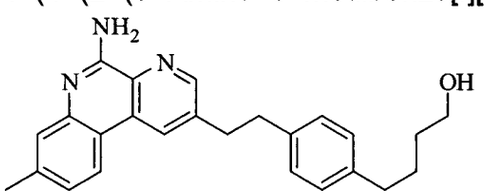
Etapa 5: 2–(2–(6–metoxi–4–metilpiridin–3–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

Se preparó 2–(2–(6–metoxi–4–metilpiridin–3–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina a partir de 2–((6–metoxi–4–metilpiridin–3–il)etinil)–8–metilbenzo[f][1,7]naftiridin–5–amina (de la etapa previa) siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 5. ^{1}H RMN ($CDCl_3$): δ 8,65 (d,

1H), 8,43 (d, 1H), 8,13 (d, 1H), 7,87 (s, 1H), 7,57 (s, 1H), 7,24 (dd, 1H), 6,60 (s, 1H), 6,39 (bs, 2H), 3,91 (s, 3H),3,17 – 3,11 (dd, 2H), 3,03 – 2,98 (dd, 2H), 2,54 (s, 3H), 2,28 (s, 3H). LRMS [M + H] = 359,2.

Ejemplo 60.

4–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)butan–1–ol.



Etapa 1: 4–(4–((trimetilsilil)etinil)fenil)but–3–in–1–ol.

Se preparó 4–(4–((trimetilsilil)etinil)fenil)but–3–in–1–ol a partir de ((4–bromofenil)etinil)trimetilsilano (comercial) y but–3–in–1–ol (comercial), siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 1.

Etapa 2: 4–(4–etinilfenil)but–3–in–1–ol.

Se preparó 4–(4–etinilfenil)but–3–in–1–ol a partir de 4–(4–((trimetilsilil)etinil)fenil)but–3–in–1–ol, siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 2.

Etapa 3: 5–((4–(4–hidroxibut–1–inil)fenil)etinil)–3–metilpicolinonitrilo.

Se preparó 5–((4–(4–hidroxibut–1–inil)fenil)etinil)–3–metilpicolinonitrilo a partir de 4–(4–etinilfenil)but–3–in–1–ol (de la etapa previa) siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 3.

Etapa 4: 4–(4–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)fenil)but–2–in–1–ol.

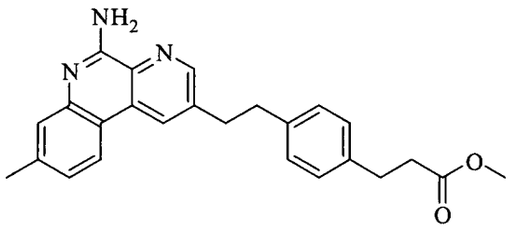
Se preparó 4–(4–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)fenil)but–2–in–1–ol a partir de 5–((4–(4–hidroxibut–1–inil)fenil)etinil)–3–metilpicolinonitrilo (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 4.

Etapa 5: 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)butan–1–ol.

Se preparó 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)butan–1–ol a partir de 4–(4–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)fenil)but–2–in–1–ol (de la etapa previa) siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 5. ^{1}H RMN ($CDCl_3$): δ 8,58 (d, 1H), 8,36 (d, 1H), 8,07 (d, 1H), 7,53 (s, 1H), 7,20 (dd, 1H), 7,10 (dd, 4H), 6,20 (bs, 2H), 3,68 (t, 2H), 3,20 – 3,15 (dd, 2H), 3,06 – 3,01 (dd, 2H), 2,64 (t, 2H), 2,52 (s, 3H), 1,75 – 1,57 (m, 4H). LRMS [M + H] = 386,2.

Ejemplo 61.

Metil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propanoato.



Etapa 1: metil 3–(4–yodofenil)propanoato.

A una solución agitada de ácido 3–(4–yodofenil)propanoico (comercial) en tolueno y metanol (9:1, 0,2 M) a 0°C, se agregó (diazometil)trimetilsilano (solución 1 N en Et_2O, 2 eq.). Después de agitar a temperatura ambiente durante la noche, la mezcla de reacción se concentró al vacío, y el residuo bruto resultante se purificó mediante la cromatografía (gel de sílice, 20–50% de EtOAc en hexanos) a fin de lograr metil 3–(4–yodofenil)propanoato.

Etapa 2: metil 3–(4–etinilfenil)propanoato.

Se preparó metil 3–(4–etinilfenil)propanoato a partir de metil 3–(4–yodofenil)propanoato (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 44/Etapas 1 y 2.

Etapa 3: metil 3–(4–((5–cloro–6–cianopiridin–3–il)etinil)fenil)propanoato.

Se preparó metil 3–(4–((5–cloro–6–cianopiridin–3–il)etinil)fenil)propanoato a partir de metil 3–(4–etinilfenil)propanoato (de la etapa previa) siguiendo los

procedimientos descriptos para el Ejemplo 44/Etapa 3.

Etapa 4: metil 3–(4–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)fenil)propanoato.

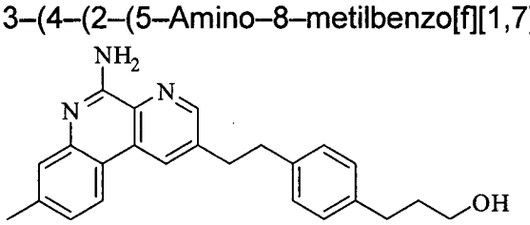
Se preparó metil 3–(4–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)fenil)propanoato a partir de metil 3–(4–((5–cloro–6–cianopiridin–3–il)etinil)fenil)propanoato (de la etapa previa) siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 4.

Etapa 5: metil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propanoato.

Se preparó metil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propanoato a partir de metil 3–(4–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)fenil)propanoato (de la etapa previa) siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 5. ^{1}H RMN (DMSO–d_6): δ 8,83 (d, 1H), 8,72 (d, 1H), 8,32 (d, 1H), 7,35 (s, 1H), 7,21–7,12 (m, 5H), 7,05 (br s, 2H), 7,05 (dd, 2H), 3,57 (s, 3H), 3,19 – 3,13 (dd, 2H), 3,06 – 3,00 (dd, 2H), 2,81 (t, 2H), 2,60 (t, 2H), 2,45 (s, 3H). LRMS [M + H] = 400,2.

Ejemplo 62.

3–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propan–1–ol.

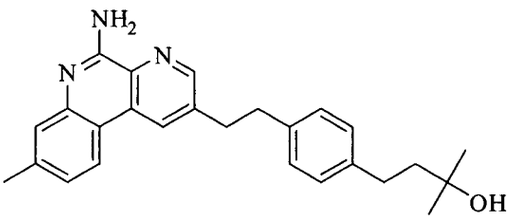


Se preparó 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propan–1–ol a partir de metil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propanoato (del Ejemplo 61) siguiendo los procedimientos descriptos para el Ejemplo 42/ Etapa 3. ^{1}H RMN de **la sal de TFA**: (DMSO–d_6): δ 9,56 (s, 1H), 9,24 (s, 1H), 8,92 (d, 1H), 8,81 (d, 1H), 8,43 (d, 1H), 7,44 (d, 1H), 7,35 (d, 1H), 7,13 (dd, 2H), 7,05 (dd, 2H), 3,32 (t, 2H), 3,18 – 3,12 (dd, 2H), 3,02 – 2,95 (dd, 2H), 2,50 (t, 2H), 2,44 (s, 3H), 1,65 – 1,57 (m, 2H).

LRMS [M + H] = 372,2.

Ejemplo 63.

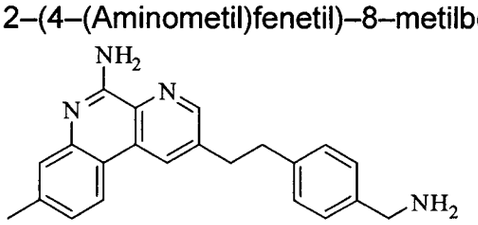
4–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)–2–metilbutan–2–ol.



A una solución de metil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propanoato (del Ejemplo 61) en THF (0,2 M) a 0°C se agregó por goteo una solución de bromuro de metilmagnesio en THF (1,0 M, 2 eq.). Después de agitar a temperatura ambiente durante la noche, la mezcla de reacción se concentró al vacío, y el residuo bruto resultante se purificó mediante la cromatografía (gel de sílice, 50–100% de EtOAc en hexanos) a fin de lograr 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)–2–metilbutan–2–ol. ^{1}H RMN ($CDCl_3$): δ 8,64 (d, 1H), 8,34 (d, 1H), 8,06 (t, 1H), 7,57 (d, 1H), 7,30 – 7,20 (m, 2H), 7,18 – 7,07 (m, 4H), 6,67 (bs, 2H), 3,24 – 3,16 (dd, 2H), 3,08 – 3,01 (dd, 2H), 2,73 – 2,66 (m, 2H), 2,53 (s, 3H), 1,82 – 1,75 (m, 2H), 1,31 (s, 3H), 1,29 (s, 3H). LRMS [M + H] = 400,2.

Ejemplo 64.

2–(4–(Aminometil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzonitrilo.

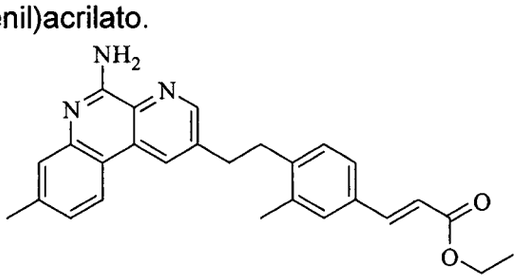
Se preparó 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzonitrilo a partir de 4–etinilbenzonitrilo (comercial) siguiendo los procedimientos descriptos para el Ejemplo 44/Etapas 3 a 5.

Etapa 2: 2–(4–(aminometil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

A una solución de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzonitrilo (de la etapa previa) en etanol e hidróxido de amonio (4:1, 0,2 M) agitada a temperatura ambiente se agregó níquel Raney (10 eq.). La mezcla de reacción se agitó en atmósfera de hidrógeno hasta la conversión completa según lo expuesto por TLC. La mezcla de reacción se filtró a través de una almohadilla corta de celite. La almohadilla de celite se lavó con EtOAc. Los extractos orgánicos combinados se concentraron al vacío, y el resido bruto resultante se purificó mediante la cromatografía (gel de sílice, 50–100% de EtOAc en hexanos) a fin de lograr el producto 2–(4–(aminometil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina. ^{1}H RMN de **la sal de TFA**: (metanol–d_4): δ 8,81 (d, 1H), 8,79 (d, 1H), 8,38 (d, 1H), 7,51 (s, 1H), 7,44 (dd, 1H), 7,36 (dd, 4H), 4,07 (s, 2H), 3,29 (s, 2H), 3,20 – 3,14 (dd, 2H), 2,55 (s, 3H). LRMS [M + H] = 343,2.

Ejemplo 65.

(E)–Etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)acrilato.



Etapa 1: (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)metanol.

Se preparó (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)metanol a partir de metil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato (Ejemplo 115), siguiendo los procedimientos descriptos para el Ejemplo 42/Etapa 3.

Etapa 2: 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzaldehído.

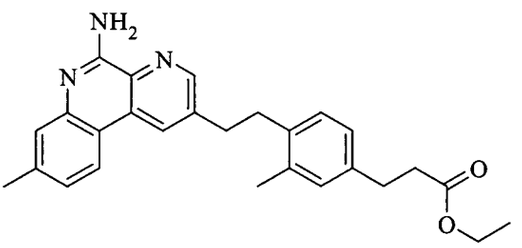
A una solución de (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)metanol (de la etapa previa) en DMSO se agregó ácido 2–yodoxibenzoico (IBX, 2,5 eq.). La reacción se agitó a temperatura ambiente durante 3 horas antes de ser diluida con agua. La extracción con EtOAc, seguida de la concentración, proporcionaron un residuo bruto que se purificó mediante la cromatografía (gel de sílice, 50–100% de EtOAc en hexanos) a fin de lograr 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzaldehído.

Etapa 3: (E)–etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)acrilato.

A una suspensión de NaH (3 eq.) en THF (0,2 M) agitada a 0°C se agregó etil 2–(dietoxifosforil)acetato (comercial) (3 eq.). Después de agitar durante 30 minutos, se agregó por goteo una solución de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzaldehído (de la etapa previa) en THF (0,2 M). La reacción se dejó entibiar hasta temperatura ambiente y se agitó durante la noche. La reacción se apagó con solución saturada de NH4Cl, y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron y se concentraron a fin de lograr un residuo bruto que se purificó por medio de la cromatografía (gel de sílice, 50–100% de EtOAc en hexanos), a fin de lograr (E)–etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)acrilato como un sólido de color blanco. ^{1}H RMN: ($CDCl_3$): δ 8,54 (d, 1H), 8,29 (d, 1H), 7,99 (d, 1H), 7,57 (d, 1H), 7,44 (s, 1H), 7,23 (dd, 1H), 7,11 (dd, 1H), 7,05 (d, 1H), 6,33 (d, 1H), 5,93 (s, 2H), 4,19 (q, 2H), 3,10 – 2,95 (m, 4H), 2,44 (s, 3H), 2,23 (s, 3H), 1,26 (t, 3H). LRMS [M + H] = 426,2.

Ejemplo 66.

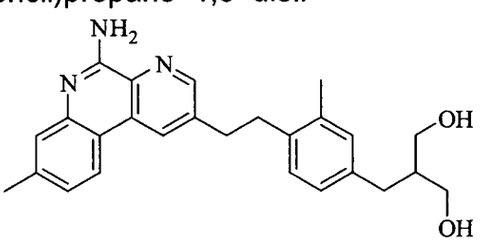
Etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propanoato.



Etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propanoato se preparó a partir de (E)–etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)acrilato (del Ejemplo 65), siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 5. ^{1}H RMN: ($CDCl_3$): δ 8,55 (d, 1H), 8,26 (d, 1H), 7,99 (d, 1H), 7,45 (s, 1H), 7,12 (dd, 1H), 6,98 –6,88 (m, 3H), 6,02 (s, 2H), 4,06 (q, 2H), 3,04 (dd, 2H), 2,93 (dd, 2H), 2,83 (t, 2H), 2,53 (t, 2H), 2,44 (s, 3H), 2,19 (s, 3H), 1,17 (t, 3H). LRMS [M + H] = 428,2.

Ejemplo 67.

2–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbencil)propano–1,3–diol.



Etapa 1: dietil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbencil)malonato.

A una solución agitada de (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)metanol (del Ejemplo 65/Etapa 1) (0,2 M) y dietil malonato (2 eq) en tolueno seco se agregaron tributilfosfina (2 eq.) y N^1,N^1,N^2,N^2–tetrametildiazeno–1,2–dicarboxamida (2 eq.). La mezcla de reacción se agitó a 120°C durante la noche. Al completarse la reacción, la mezcla de reacción se concentró al vacío, y el residuo bruto resultante se purificó por medio de la cromatografía (gel de sílice, 50–100% de EtOAc en hexanos) a fin de lograr dietil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbencil)malonato

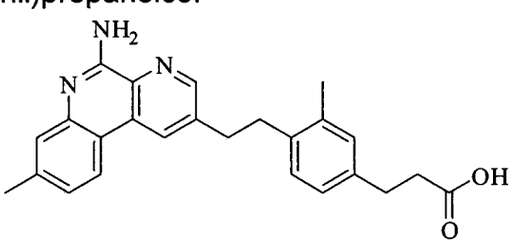
como un sólido de color blanco.

Etapa 2: 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbencil)propano–1,3–diol.

Se preparó 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbencil)propano–1,3–diol a partir de dietil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbencil)malonato (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 42/Etapa 3. ^{1}H RMN: (metanol–d_4): δ 8,51 (d, 1H), 8,39 (d, 1H), 8,05 (d, 1H), 7,45 (s, 1H), 7,10 (dd, 1H), 6,91 –6,87 (m, 2H), 6,83 (dd, 1H), 3,42 (d, 4H), 3,08 – 3,02 (m, 2H), 2,96 – 2,91 (m, 2H), 2,47 (d, 2H), 2,38 (s, 3H), 2,13 (s, 3H). LRMS [M + H] = 416,2.

Ejemplo 68.

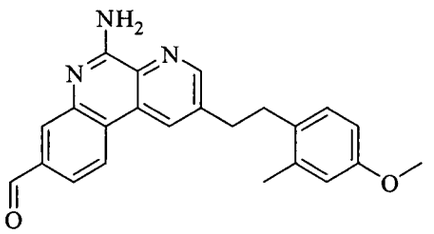
Ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propanoico.



Una solución de etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propanoato (del Ejemplo 66) en NaOH, 1 N, THF y metanol (1:5:2, 0,1 N) se calentó a 60°C durante 3 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se neutralizó con HCl, 1 N, hasta pH 7, y se concentró a fin de lograr un residuo bruto que se purificó mediante la cromatografía (gel de sílice, 0–20% de metanol en diclorometano) de manera de obtener (E)–etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)acrilato como un sólido de color blanco. ^{1}H RMN: (metanol–d_4): δ 8,73 (d, 1H), 8,54 (d, 1H), 8,20 (d, 1H), 7,45 (s, 1H), 7,37 (d, 1H), 7,00 –6,97 (m, 2H), 6,92 (d, 1H), 3,19 (t, 2H), 3,04 (t, 2H), 2,81 (t, 2H), 2,53 (t, 2H), 2,50 (s, 3H), 2,25 (s, 3H). LRMS [M + H] = 400,2.

Ejemplo 69.

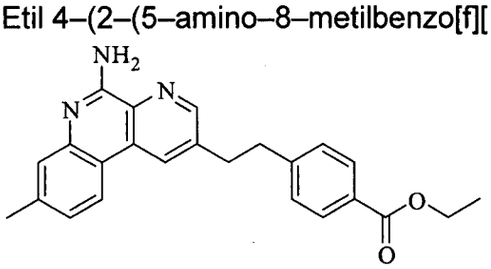
5–Amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridina–8–carbaldehído.



Se preparó 5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridina–8–carbaldehído a partir de (5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)metanol (del Ejemplo 108) siguiendo los procedimientos descriptos para el Ejemplo 65/Etapa 2. ^{1}H RMN: ($CDCl_3$): δ 10,19 (s, 1H), 8,74 (d, 1H), 8,43 (d, 1H), 8,32 (d, 1H), 8,18 (d, 1H), 7,88 (dd, 1H), 7,00 (d, 1H), 6,76 (d, 1H), 6,70 (dd, 1H), 6,30 (s, 2H), 3,80 (s, 3H), 3,16 (dd, 2H), 3,02 (dd, 2H), 2,29 (s, 3H). LRMS [M + H] = 372,2.

Ejemplo 70.

Etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoato.



Etapa 1: etil 4–((5–cloro–6–cianopiridin–3–il)etiníl)benzoato.

Una solución de 3,5–dicloropicolinonitrilo (comercial) (1,0 eq.), etil 4–etinilbenzoato (comercial) (1,0 eq.), trans–diclororbis(trifenilfosfina)paladio (II) (10% en moles), yoduro de cobre (I) (20% en moles) y trietilamina (5,0 eq.) en DMF (0,3 M) se agitó a 50°C durante 3 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo e hidróxido de amonio acuoso al 10%. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se

lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–20% de acetato de etilo en hexano, a fin de lograr etil 4–((5–cloro–6–cianopiridin–3–il)etinil)benzoato como un sólido de color blanco.

Etapa 2: etil 4–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)benzoato.

Una solución de etil 4–((5–cloro–6–cianopiridin–3–il)etinil)benzoato (de la etapa previa) (1,0 eq.), ter–butil 5–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (del Ejemplo 5/Etapa 2) (2,6 eq.), tetraquis(trifenilfosfina)paladio (10% en moles) y carbonato de potasio (5,3 eq.) en tolueno/etanol (2:1, 0,2 M) se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con 2% de MeOH en DCM. Se separaron las dos fases. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–40% de acetato de etilo en tolueno, a fin de lograr etil 4–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)benzoato.

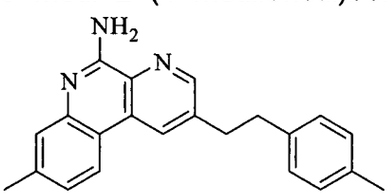
Etapa 3: etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoato.

Una solución de etil 4–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)benzoato (de la etapa previa) (1,0 eq.) en THF/etil acetato (1:1, 0,05 M) se inundó con nitrógeno, y se agregó paladio sobre carbón (10% en peso). El recipiente de reacción se evacuó, se inundó con hidrógeno y se agitó durante la noche a temperatura ambiente. La mezcla de reacción se filtró a través de celite, se lavó con 2% de MeOH en DCM, y se concentró al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de MeOH en DCM, a fin de lograr etil 4–(2–(5–amino–8–

metilbenzo[f][1,7]naftiridin–2–il)etil)benzoato. ^{1}H RMN (Acetona– d_6): δ 8,80 (s, 1H), 8,69 (s, 1H), 8,25 (d, 1H), 7,90 (d, 2H), 7,40–7,42 (m, 3H), 7,12 (d, 1H), 6,55 (br, 2H), 4,28 (q, 2H), 3,2–3,3 (m, 4H), 2,44 (s, 3H), 1,31 (t, 3H). LRMS [M + H] = 386,2.

Ejemplo 71.

8–Metil–2–(4–metilfenetil)benzo[f][1,7]naftiridin–5–amina.



Etapa 1: 3–cloro–5–(p–toliletinil)picolinonitrilo.

Una solución de 3,5–dicloropicolinonitrilo (comercial) (1,0 eq.), 1–etinil–4–metilbenceno (comercial) (1,0 eq.), trans–diclororbis(trifenilfosfina)paladio (II) (10% en moles), yoduro de cobre (I) (20% en moles) y trietilamina (5,0 eq.) en DMF (0,3 M) se agitó a 50°C durante 3 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo y 10% de hidróxido de amonio acuoso. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la agitación en mezclas de éter caliente/hexano y se filtró, a fin de lograr 3–cloro–5–(p–toliletinil)picolinonitrilo.

Etapa 2: 8–metil–2–(p–toliletinil)benzo[f][1,7]naftiridin–5–amina.

Una solución de 3–cloro–5–(p–toliletinil)picolinonitrilo (de la etapa previa) (1,0 eq.), ter–butil 5–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (del Ejemplo 5/Etapa 2) (1,2 eq.), tetraquis(trifenilfosfina)paladio (10% en moles), y solución acuosa de carbonato de sodio, 2 N, (4,0 eq.) en tolueno/etanol (2:1, 0,2 M) se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con 2% de MeOH en DCM. Se separaron las dos fases, y la capa acuosa se extrajo con 2% de MeOH

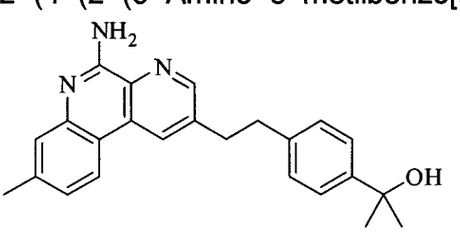
en DCM, dos veces. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–40% de acetato de etilo en tolueno, a fin de lograr 8–metil–2–(p–toliletinil)benzo[f][1,7]naftiridin–5–amina.

Etapa 3: 8–metil–2–(4–metilfenetil)benzo[f][1,7]naftiridin–5–amina.

Una solución de 8–metil–2–(p–toliletinil)benzo[f][1,7]naftiridin–5–amina (de la etapa previa) (1,0 eq.) en EtOH/acetato de etilo (1:1, 0,05 M) se inundó con nitrógeno, y se agregó paladio sobre carbón (10% en peso). El recipiente de reacción se evacuó, se inundó con hidrógeno, y se agitó durante la noche a temperatura ambiente. La mezcla de reacción se filtró a través de celite, se lavó con 2% de MeOH en DCM, y se concentró al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de MeOH en DCM a fin de lograr 8–metil–2–(4–metilfenetil)benzo[f][1,7]naftiridin–5–amina. ^{1}H RMN (Acetona– d_6): δ 8,74 (s, 1H), 8,68 (s, 1H), 8,24 (d, 1H), 7,41 (s, 1H), 7,13–7,15 (m, 3H), 7,06 (d, 2H), 6,6 (br, 2H), 3,19 (t, 2H), 3,06 (t, 2H), 2,44 (s, 3H), 2,25 (s, 3H). LRMS [M + H] = 328,1.

Ejemplo 72.

2–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propan–2–ol.

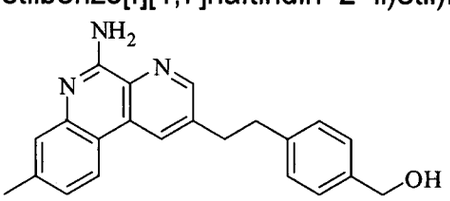


A una solución de etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoato (del Ejemplo 70) (1,0 eq.) en DCM a 0°C se agregó yoduro de metil magnesio, 3,0 M (10 eq.), en éter, y se entibió hasta temperatura ambiente durante la noche. La reacción se enfrió hasta 0°C y se apagó con solución acuosa de HCl, 1 N, y éter. Después de agitar durante 15 minutos, la mezcla de reacción

se neutralizó con solución de bicarbonato de sodio acuoso saturado. Se separaron las dos fases, y la capa acuosa se extrajo con éter. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la RP–HPLC usando un gradiente de 10–50% de MeCN en agua, seguido de la extracción en DCM a fin de lograr 2–(4–(2–(5–amino–8 metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propan–2–ol. ^{1}H RMN (Acetona– d_6): δ 8,73 (m, 2H), 8,22 (d, 1H), 7,40–7,44 (m, 3H), 7,20 (d, 2H), 7,12 (d, 1H), 6,5 (br, 2H), 3,94 (s, 1H), 3,21 (t, 2H), 3,08 (t, 2H), 2,44 (s, 3H), 1,47 (s, 6H). LRMS [M + H] = 372,2.

Ejemplo 73.

(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)metanol.

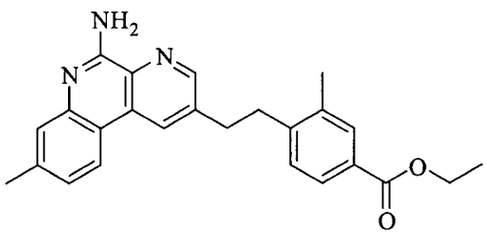


A una solución de etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoato (Ejemplo 70) (1,0 eq.) en THF (0,1 M) a 0°C se agregó trietilborohidruro de litio, 1,0 M, en THF (10 eq.), y se entibió hasta temperatura ambiente en un lapso de 2 horas. Se agregó lentamente solución acuosa de HCl, 1 N, de modo de apagar la reacción, y la mezcla se calentó hasta reflujo durante 30 minutos. La mezcla de reacción se neutralizó con solución de bicarbonato de sodio acuoso saturado. Se separaron las dos fases, y la capa acuosa se extrajo con acetato de etilo (EA). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la RP–HPLC usando un gradiente de 10–50% de MeCN en agua, seguido de la extracción en DCM, a fin de lograr (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)metanol. ^{1}H RMN (Acetona–d_6): δ 8,77 (s, 1H), 8,69 (s, 1H), 8,26 (d, 1H), 7,40 (s, 1H), 7,21–7,28 (m, 4H), 7,13

(d, 1H), 6,5 (br, 2H), 4,56 (s, 2H), 4,1 (br t, 1H), 3,10–3,23 (m, 4H), 2,44 (s, 3H). LRMS [M + H] = 344,2.

Ejemplo 74.

Etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato.



Etapa 1: etil 4–bromo–3–metilbenzoato.

A una solución de ácido 4–bromo–3–metilbenzoico (comercial) (1,0 eq.) en EtOH (0,3 M) se agregó cloruro de tionilo (1,5 eq.), y la solución se calentó hasta reflujo durante 2 horas. El solvente se concentró al vacío, y el residuo se diluyó en éter y se neutralizó con solución de bicarbonato de sodio acuoso saturado. Se separaron las dos fases, y la capa acuosa se extrajo con éter. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío, a fin de lograr etil 4–bromo–3–metilbenzoato.

Etapa 2: etil 3–metil–4–((trietilsilil)etinil)benzoato.

Una solución de etil 4–bromo–3–metilbenzoato (de la etapa previa) (1,0 eq.), trietil(etinil)silano (1,1 eq.), trans–diclororbis(trifenilfosfina)paladio (II) (10% en moles), yoduro de cobre (I) (20% en moles) y trietilamina (5,0 eq.) en DMF (0,3 M) se agitó a 60°C durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo e hidróxido de amonio acuoso al 10%. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de acetato de etilo en hexano, a fin de

lograr etil 3–metil–4–((trietilsilil)etinil)benzoato en forma de un aceite de color amarillo.

Etapa 3: etil 4–etinil–3–metilbenzoato.

A una solución de etil 3–metil–4–((trietilsilil)etinil)benzoato (de la etapa previa) (1,0 eq.) en THF (0,3 M) a 0°C se agregó, por goteo, TBAF, 1,0 M, en THF (1,2 eq.). Después de agitar un período de tiempo de 10 minutos a 0°C, la reacción se apagó con solución de bicarbonato de sodio acuoso saturado. Se separaron las dos fases, y la capa acuosa se extrajo con éter. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de acetato de etilo en hexano a fin de lograr etil 4–etinil–3–metilbenzoato como un sólido de color blanco.

Etapa 4: etil 4–((5–cloro–6–cianopiridin–3–il)etinil)–3–metilbenzoato.

Una solución de 3,5–dicloropicolinonitrilo (1,0 eq.), etil 4–etinil–3–metilbenzoato (de la etapa previa) (1,0 eq.), trans–diclororbis(trifenilfosfina)paladio (II) (10% en moles), yoduro de cobre (I) (20% en moles) y trietilamina (5,0 eq.) en DMF (0,3 M) se agitó a 50°C durante 3 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo e hidróxido de amonio acuoso al 10%. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–10% de acetato de etilo en hexano, a fin de lograr etil 4–((5–cloro–6–cianopiridin–3–il)etinil)–3–metilbenzoato como un sólido de color blanco.

Etapa 5: etil 4–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)–3–metilbenzoato.

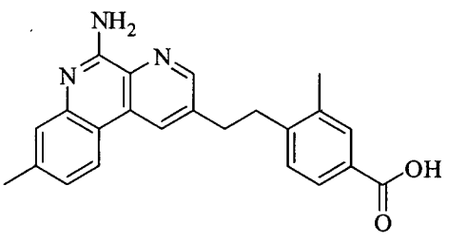
Una solución de etil 4–((5–cloro–6–cianopiridin–3–il)etinil)–3–metilbenzoato (de la etapa previa) (1,0 eq.), ter–butil 5–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (del Ejemplo 5/Etapa 2) (1,1 eq.), tetraquis(trifenilfosfina)paladio (8% en moles) y carbonato de potasio (3,0 eq.) en tolueno/etanol (9:1, 0,2 M) se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con 2% de MeOH en DCM. Se separaron las dos fases. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–40% de acetato de etilo en tolueno, a fin de lograr etil 4–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)–3–metilbenzoato.

Etapa 6: etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato.

Una solución de etil 4–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)–3–metilbenzoato (de la etapa previa) (1,0 eq.) en THF/etil acetato (1:1, 0,05 M) se inundó con nitrógeno y se le agregó paladio sobre carbón al 10% (10% en peso). El recipiente de reacción se evacuó, se inundó con hidrógeno, y se agitó durante la noche a temperatura ambiente. La mezcla de reacción se filtró a través de celite, se lavó con 2% de MeOH en DCM, y se concentró al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 30–100% de EA en hexano, a fin de lograr etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato. ^1H RMN (Acetona– d_6): δ 8,79 (s, 1H), 8,71 (s, 1H), 8,24 (d, 1H), 7,80 (s, 1H), 7,73 (d, 1H), 7,40 (s, 1H), 7,31 (d, 1H), 7,12 (d, 1H), 6,5 (br, 2H), 4,29 (q, 2H), 3,19–3,22 (m, 4H), 2,44 (s, 3H), 2,39 (s, 3H), 1,31 (t, 3H). LRMS [M + H] = 400,2.

Ejemplo 75.

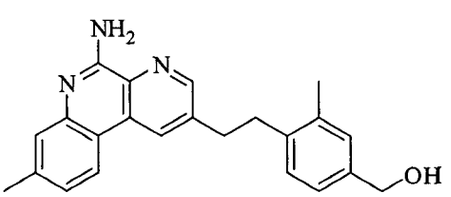
Ácido 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoico.



A una solución de etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato (del Ejemplo 74) (1,0 eq.) en EtOH se agregó hidróxido de sodio acuoso, 1 N (1,5 eq.), y la solución se calentó hasta 80°C un lapso de 5 horas. La mezcla de reacción se neutralizó mediante la adición de HCl acuoso, 1 N (1,5 eq.) y se concentró al vacío. El material bruto se purificó por medio de la RP–HPLC usando un gradiente de 10–50% de MeCN en agua, seguido de la concentración al vacío, a fin de lograr la sal de TFA. ^{1}H RMN (DMSO– d_6) de **la sal de TFA**: δ 7,94–7,96 (m, 2H), 7,55 (d, 1H), 7,00 (s, 1H), 6,91 (d, 1H), 6,62–6,66 (m, 2H), 6,39 (d, 1H), 2,36–2,5 (m, 4H), 1,73 (s, 3H), 1,54 (s, 3H). LRMS [M + H] = 372,2.

Ejemplo 76.

(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)metanol.

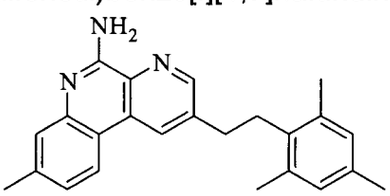


A una solución de etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato (del Ejemplo 74) (1,0 eq.) en THF (0,1 M) a –78°C se agregó DIBAL, 1,0 M, en tolueno (10 eq.), y la solución se entibió hasta temperatura ambiente en un período de tiempo de 2 horas. Se agregó solución acuosa de la sal de Rochelle, 1,5 M, lentamente, a fin de apagar la reacción; a

continuación, se agregó EA, y la mezcla se agitó durante 45 minutos. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con EA. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la RP–HPLC usando un gradiente de 10–50% de MeCN en agua, seguido de la extracción en DCM, a fin de lograr (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)metanol. ^{1}H RMN (Acetona– d_6): δ 8,77 (s, 1H), 8,71 (s, 1H), 8,25 (d, 1H), 7,41 (s, 1H), 7,10–7,15 (m, 4H), 6,5 (br, 2H), 4,54 (s, 2H), 4,05 (br, 1H), 3,08–3,18 (m, 4H), 2,44 (s, 3H), 2,31 (s, 3H). LRMS [M + H] = 358,2.

Ejemplo 77.

8–Metil–2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina.



Etapa 1: 3–cloro–5–(mesitiletinil)picolinonitrilo.

Una solución de 3,5–dicloropicolinonitrilo (1,0 eq.), 2–etinil–1,3,5–trimetilbenceno (comercial) (1,0 eq.), trans–diclororbis(trifenilfosfina)paladio (II) (10 % en moles), yoduro de cobre (I) (20% en moles) y trietilamina (5,0 eq.) en DMF (0,3 M) se agitó a 50°C durante 3 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo e hidróxido de amonio acuoso al 10%. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–10% de acetato de etilo en hexano, a fin de lograr 3–cloro–5–(mesitiletinil)picolinonitrilo en forma de un sólido de color blanco.

Etapa 2: 2–(mesitiletinil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

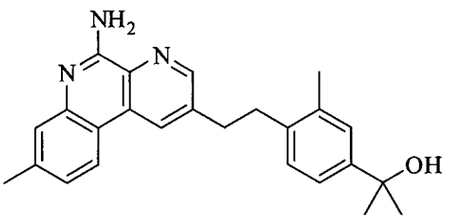
Una solución de 3–cloro–5–(mesitiletinil)picolinonitrilo (de la etapa previa) (1,0 eq.), ter–butil 5–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (del Ejemplo 5/Etapa 2) (1,1 eq.), tetraquis(trifenilfosfina)paladio (8% en moles) y solución acuosa de carbonato de sodio, 2 N (3,0 eq.) en tolueno/etanol (4:1, 0,2 M) se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con 2% de MeOH en DCM. Se separaron las dos fases. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–40% de acetato de etilo en tolueno, a fin de lograr 2–(mesitiletinil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

Etapa 3: 8–metil–2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina.

Una solución de 2–(mesitiletinil)–8–metilbenzo[f][1,7]naftiridin–5–amina (de la etapa previa) (1,0 eq.) en EtOH (0,05 M) se inundó con nitrógeno. y se le agregó paladio sobre carbón (10% en peso). El recipiente de reacción se evacuó, se inundó con hidrógeno, y se agitó durante la noche a t. a. La mezcla de reacción se filtró a través de celite, se lavó con 2% de MeOH en DCM, y se concentró al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–50% de acetato de etilo en hexano, a fin de lograr 8–metil–2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina. ^1H RMN (Acetona– d_6): δ 8,73–8,74 (m, 2H), 8,25 (d, 1H), 7,42 (s, 1H), 7,14 (d, 1H), 6,83 (s, 2H), 6,55 (br, 2H), 3,07 (m, 4H), 2,47 (s, 3H), 2,29 (s, 6H), 2,22 (s, 3H), LRMS [M + H] = 356,2.

Ejemplo 78.

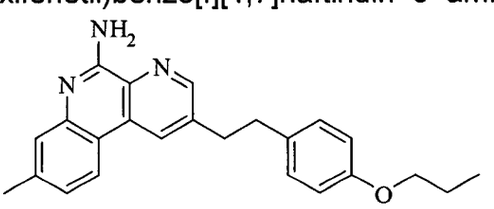
2–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol.



A una solución de etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato (del Ejemplo 74) (1,0 eq.) en DCM a 0°C se agregó yoduro de metil magnesio, 3,0 M (10 eq.) en éter, y la solución se entibió hasta temperatura ambiente durante la noche. La reacción se enfrió hasta 0°C y se apagó con agua. Después de agitar un período de tiempo de 15 min, la mezcla de reacción se neutralizó con solución de bicarbonato de sodio acuoso saturado, y se le agregó EA. Se separaron las dos fases, y la capa acuosa se extrajo tres veces con EA. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de MeOH en DCM, a fin de lograr 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol. ^{1}H RMN (Acetona–d_6): δ 8,72–8,75 (m, 2H), 8,23 (d, 1H), 7,41 (s, 1H), 7,32 (s, 1H), 7,25 (d, 1H), 7,12–7,14 (m, 2H), 6,6 (br, 2H), 3,91 (s, 1H), 3,07–3,18 (m, 4H), 2,44 (s, 3H), 2,31 (s, 3H), 1,48 (s, 6H). LRMS [M + H] = 386,2.

Ejemplo 79.

8–Metil–2–(4–propoxifenetil)benzo[f][1,7]naftiridin–5–amina.



Etapa 1: 3–cloro–5–((4–propoxifenil)etinil)picolinonitrilo.

Una solución de 3,5–dicloropicolinonitrilo (1,0 eq.), 1–etinil–4–propoxibenceno (comercial) (1,0 eq.), trans–diclororbis(trifenilfosfina)paladio (II) (10% en moles), yoduro de cobre (I) (20% en moles) y trietilamina (5,0 eq.) en

DMF (0,3 M) se agitó a 50°C durante 3 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo e hidróxido de amonio acuoso al 10%. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–10% de acetato de etilo en hexano, a fin de lograr 3–cloro–5–((4–propoxifenil)etinil)picolinonitrilo como un sólido de color blanco.

Etapa 2: 3–cloro–5–(4–propoxifenetil)picolinonitrilo.

Una solución de 3–cloro–5–((4–propoxifenil)etinil)picolinonitrilo (de la etapa previa) (1,0 eq.) en EtOH (0,05 M) se inundó con nitrógeno, y se le agregó óxido de platino (VI) (0,5 eq.). El recipiente de reacción se evacuó, se inundó con hidrógeno, y se agitó durante 5 horas a temperatura ambiente. La mezcla de reacción se filtró a través de celite, se lavó con 2% de MeOH en DCM, y se concentró al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–15% de acetato de etilo en hexano, a fin de lograr 3–cloro–5–(4–propoxifenetil)picolinonitrilo.

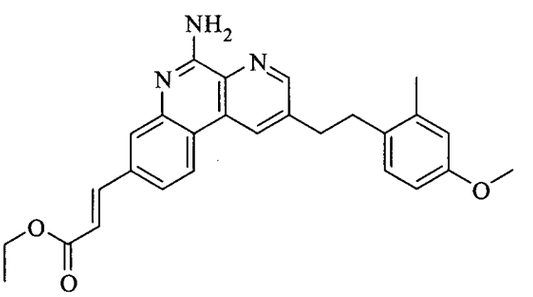
Etapa 3: 8–metil–2–(4–propoxifenetil)benzo[f][1,7]naftiridin–5–amina.

Una solución de 3–cloro–5–(4–propoxifenetil)picolinonitrilo (de la etapa previa) (1,0 eq.), ter–butil 5–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (del Ejemplo 5/Etapa 2) (1,1 eq.), tetraquis(trifenilfosfina)paladio (8% en moles) y solución acuosa de carbonato de sodio, 2 N (3,0 eq.), en tolueno (0,2 M), se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con 2% de MeOH en DCM. Se separaron las dos fases. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El

material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–40% de acetato de etilo en tolueno, a fin de lograr 8–metil–2–(4–propoxifenetil)benzo[f][1,7]naftiridin–5–amina. ^{1}H RMN (Acetona– d_6): δ 8,74 (s, 1H), 8,67 (s, 1H), 8,24 (d, 1H), 7,41 (s, 1H), 7,15–7,17 (m, 3H), 6,81 (d, 2H), 6,5 (br, 2H), 3,87 (t, 2H), 3,18 (t, 2H), 3,04 (t, 2H), 2,44 (s, 3H), 1,73 (m, 2H), 0,99 (t, 3H). LRMS [M + H] = 372,2.

Ejemplo 80.

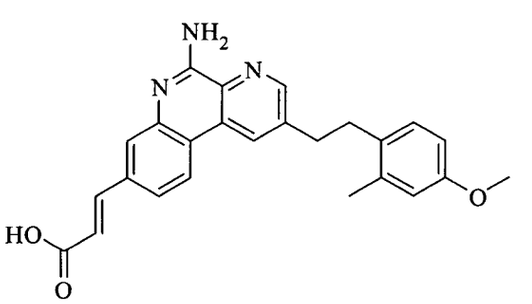
(E)–Etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)acrilato.



Se preparó (E)–etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)acrilato a partir de 5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridina–8–carbaldehído (del Ejemplo 69) y etil 2–(dietoxifosforil)acetato (comercial), siguiendo los procedimientos descriptos para el Ejemplo 65/Etapa 3. LRMS [M + H] = 442,2.

Ejemplo 81.

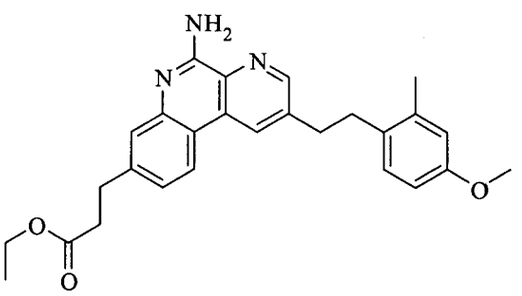
Ácido (E)–3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)acrílico.



Se preparó ácido (E)–3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)acrílico a partir de (E)–etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)acrilato (del Ejemplo 80), siguiendo los procedimientos descriptos para el Ejemplo 68. ^{1}H RMN de **la sal de TFA** (DMSO– d_6): δ 12,66 (s, 1H), 9,09 (s, 1H), 8,88 (s, 1H), 8,66 (d, 1H), 7,95 (d, 1H), 7,91 (s, 1H), 7,75 (d, 1H), 7,10 (d, 1H), 6,77 – 6,71 (m, 2H), 6,68 (dd, 1H), 3,70 (s, 3H), 3,16 (t, 2H), 3,00 (t, 2H), 2,30 (s, 3H). LRMS [M + H] = 414,2.

Ejemplo 82.

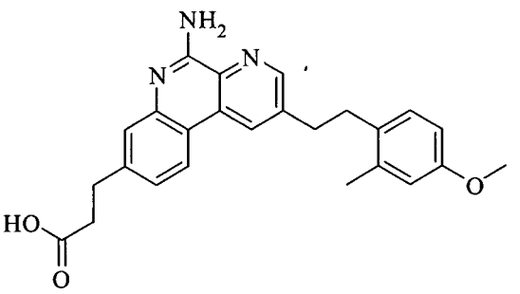
Etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propanoato.



Se preparó etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propanoato a partir de (E)–etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)acrilato (del Ejemplo 80), siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 5. ^{1}H RMN ($CDCl_3$): δ 8,63 (d, 1H), 8,37 (d, 1H), 8,13 (d, 1H), 7,56 (d, 1H), 7,24 (dd, 1H), 7,02 (d, 1H), 6,75 (d, 1H), 6,69 (dd, 1H), 6,15 (br s, 2H), 4,17 (q, 2H), 3,79 (s, 3H), 3,12 (dd, 4H), 2,99 (dd, 2H), 2,75 (t, 2H), 2,29 (s, 3H), 1,27 (t, 2H), 0,99 (t, 3H). LRMS [M + H] = 444,2.

Ejemplo 83.

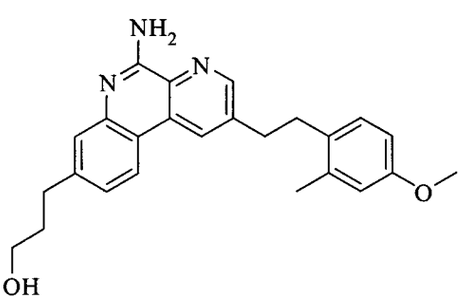
Ácido 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propanoico.



Se preparó ácido 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propanoico a partir de etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propanoato (del Ejemplo 82), siguiendo los procedimientos descriptos para el Ejemplo 68. ^{1}H RMN (DMSO– d_6): δ 12,18 (s, 1H), 8,84 (d, 1H), 8,70 (d, 1H), 8,36 (d, 1H), 7,39 (d, 1H), 7,20 (dd, 1H), 7,09 (m, 2H), 6,74 (d, 1H), 6,68 (dd, 1H), 3,70 (s, 3H), 3,09 (dd, 2H), 2,96 (dd, 4H), 2,63 (t, 2H), 2,27 (s, 3H). LRMS [M + H] = 416,2.

Ejemplo 84.

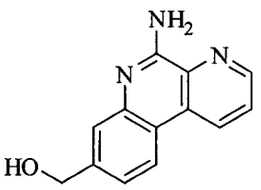
3–(5–Amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propan–1–ol.



Se preparó 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propan–1–ol a partir de etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propanoato (del Ejemplo 82), siguiendo los procedimientos descriptos para el Ejemplo 42/Etapa 3. ^{1}H RMN ($CDCl_3$): δ 8,54 (d, 1H), 8,30 (d, 1H), 8,05 (d, 1H), 7,48 (d, 1H), 7,15 (dd, 1H), 6,93 (d, 1H), 6,66 (d, 1H), 6,61 (dd, 1H), 5,98 (br s, 2H), 3,71 (s, 3H), 3,66 (t, 2H), 3,03 (dd, 2H), 2,91 (dd, 2H), 2,81 (t, 2H), 2,20 (s, 3H), 1,98 – 1,90 (m, 2H). LRMS [M + H] = 402,2.

Ejemplo 85.

(5–Aminobenzo[f][1,7]naftiridin–8–il)metanol.



Etapa 1: ácido 2–(ter–butoxicarbonilamino)–4–(metoxicarbonil)fenilbórico.

Una solución de clorhidrato de ácido 2–amino–4–(metoxicarbonil)fenilbórico (comercial) (1,0 eq.), trietilamina (3,0 eq.), di–*ter*–butil dicarbonato (1,1 eq.) y DMAP (0,1 eq.) en CH_3CN (0,3 M) se agitó a 40°C durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se concentró al vacío de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–30% de MeOH/DCM, a fin de lograr ácido 2–(ter–butoxicarbonilamino)–4–(metoxicarbonil)fenilbórico en forma de un sólido de color marrón.

Etapa 2: metil 5–aminobenzo[f][1,7]naftiridina–8–carboxilato.

Una solución de ácido 2–(*ter*–butoxicarbonilamino)–4–(metoxicarbonil) fenilbórico (de la etapa previa) (1,0 eq.) y 3–bromopicolinonitrilo (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (2,0 eq.) en tolueno/etanol (2:1, 0,03 M) se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se filtró, de manera de recoger el precipitado. El precipitado se enjuagó con EtOAc, a fin de lograr metil 5–aminobenzo[f][1,7]naftiridina–8–carboxilato en forma de un sólido de color marrón pálido.

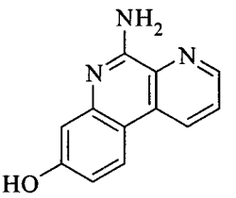
Etapa 3: (5–aminobenzo[f][1,7]naftiridin–8–il)metanol.

A una solución de metil 5–aminobenzo[f][1,7]naftiridina–8–carboxilato (de la etapa previa) (1,0 eq.) en EtOH (0,03 M) se agregó $NaBH_4$ (10 eq.) a 25°C. La solución se calentó hasta 80°C durante 5 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se concentró al vacío. El residuo se fraccionó entre $NaHCO_3$ saturado y EtOAc. Se separaron las capas, y la capa

acuosa se extrajo con EtOAc, dos veces. La capa orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío, de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–10% de MeOH/DCM, a fin de lograr (5–aminobenzo[f][1,7]naftiridin–8–il)metanol como un sólido blanquecino. ^{1}H RMN (metanol– d_4): δ 8,82 (dd, 1H), 8,77 (dd, 1H), 7,26 (d, 1H), 7,70 (dd, 1H), 7,50(d, 1H), 7,27 (dd, 1H), 4,66 (s, 2H). LRMS [M + H] = 226,1.

Ejemplo 86.

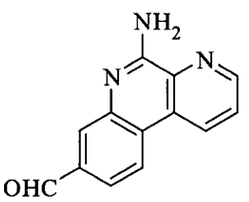
5–Aminobenzo[f][1,7]naftiridin–8–ol.



A una solución de 8–metoxibenzo[f][1,7]naftiridin–5–amina (del Ejemplo 10) (1,0 eq.) en DCM (0,04 M) se agregó BBr_3 (2,5 eq.), por goteo, bajo N_2 a –20°C. La reacción se dejó entibiar hasta temperatura ambiente en un período de tiempo de 30 minutos. La reacción entonces se agitó durante la noche. La reacción se apagó con $NaHCO_3$ saturado y se extrajo con EtOAc. La capa orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío, de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–20% de MeOH/DCM, a fin de lograr 5–aminobenzo[f][1,7]naftiridin–8–ol en forma de un sólido de color amarillo. ^{1}H RMN (acetona– d_6): δ 8,90 (dd, 1H), 8,83 (dd, 1H), 8,32 (d, 1H), 7,83 (dd, 1H), 7,11 (br s, 2H), 7,10(d, 1H), 6,96 (dd, 1H), 5,86 (br s, 1H). LRMS [M + H] = 212,1.

Ejemplo 87.

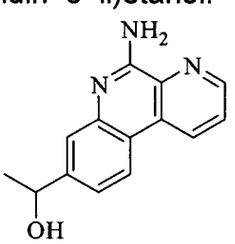
5–Aminobenzo[f][1,7]naftiridina–8–carbaldehído.



Una solución de (5–aminobenzo[f][1,7]naftiridin–8–il)metanol (del Ejemplo 85) (1,0 eq.) y MnO_2 activado (20 eq.) en DCM (0,1 M) se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con DCM. El MnO_2 se separó mediante la filtración, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–10% de MeOH/DCM, a fin de lograr 5–aminobenzo[f][1,7]naftiridina–8–carbaldehído en forma de un sólido de color amarillo. ^{1}H RMN (acetona– d_6): δ 10,19 (s, 1H), 9,14 (dd, 1H), 9,01 (dd, 1H), 8,63 (d, 1H), 8,14 (d, 1H), 7,93(dd, 1H), 7,81 (dd, 1H), 6,96 (br s, 2H). LRMS [M + H] = 224,1.

Ejemplo 88.

1–(5–Aminobenzo[f][1,7]naftiridin–8–il)etanol.

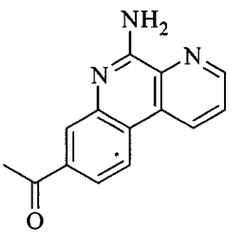


A una solución de 5–aminobenzo[f][1,7]naftiridina–8–carbaldehído (del Ejemplo 87) (1,0 eq.) en THF (0,02 M) se agregó MeLi (2,5 eq.) a –78°C. La reacción se dejó entibiar hasta temperatura ambiente durante la noche. La reacción se apagó con NH_4Cl saturado y se extrajo con EtOAc. La capa orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de MeOH/DCM, a fin de lograr 1–(5–aminobenzo[f][1,7]naftiridin–8–il)etanol en forma de un sólido de color amarillo. ^{1}H RMN (metanol– d_4): δ 8,94 (dd, 1H), 8,88

(dd, 1H), 8,38 (d, 1H), 7,81 (dd, 1H), 7,62(d, 1H), 7,41 (dd, 1H), 4,97 (q, 1H), 1,53 (d, 3H). LRMS [M + H] = 240,1.

Ejemplo 89.

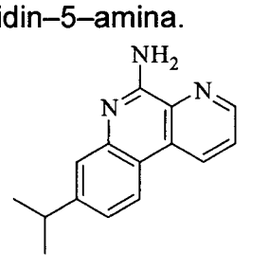
1–(5–Aminobenzo[f][1,7]naftiridin–8–il)etanona.



Una solución 1–(5–aminobenzo[f][1,7]naftiridin–8–il)etanol (del Ejemplo 88) (1,0 eq.) y MnO_2 activado (20 eq.) en DCM (0,1 M) se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con DCM. El MnO_2 se separó mediante la filtración, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de MeOH/DCM, a fin de lograr 1–(5–aminobenzo[f][1,7]naftiridin–8–il)etanona en forma de un sólido de color amarillo. ^{1}H RMN (acetona– d_6): δ 9,11(dd, 1H), 8,99 (dd, 1H), 8,56 (d, 1H), 8,20 (d, 1H), 7,94–7,88(m, 2H), 6,90 (br s, 2H), 2,70 (s, 3H). LRMS [M + H] = 238,1.

Ejemplo 90.

8–Isopropilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 2–(5–aminobenzo[f][1,7]naftiridin–8–il)propan–2–ol.

A una solución de metil 5–aminobenzo[f][1,7]naftiridina–8–carboxilato (del Ejemplo 85/Etapa 2) (1,0 eq.) en THF (0,02 M) se agregó MeLi (10 eq.) a –78°C. La reacción se dejó entibiar hasta temperatura ambiente durante la noche. La

reacción se apagó con NH_4Cl saturado y se extrajo con EtOAc. La capa orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío, de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–10% de MeOH/DCM, a fin de lograr 2–(5–aminobenzo[f][1,7]naftiridin–8–il)propan–2–ol en forma de un aceite de color amarillo.

Etapa 2: 8–(prop–1–en–2–il)benzo[f][1,7]naftiridin–5–amina.

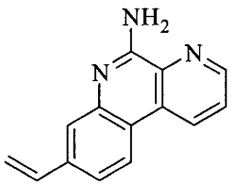
Una solución de 2–(5–aminobenzo[f][1,7]naftiridin–8–il)propan–2–ol (de la etapa previa) (1,0 eq.) y *p*–TsOH (2 eq.) en tolueno (0,01 M) se agitó a 90°C durante 6 horas. La reacción se apagó con $NaHCO_3$ saturado y se extrajo con EtOAc. La capa orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío, de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de MeOH/DCM, a fin de lograr 8–(prop–1–en–2–il)benzo[f][1,7]naftiridin–5–amina en forma de un sólido de color amarillo.

Etapa 3: 8–isopropilbenzo[f][1,7]naftiridin–5–amina.

Una mezcla de 8–(prop–1–en–2–il)benzo[f][1,7]naftiridin–5–amina (de la etapa previa) (1,0 eq) y Pd/C (húmedo, 10% en peso) en EtOH se agitó bajo un balón de H_2 durante la noche. La mezcla de reacción se diluyó con DCM. El Pd/C se separó mediante la filtración a través de celite, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–60% de EtOAc/Hexanos, a fin de lograr 8–isopropilbenzo[f][1,7]naftiridin–5–amina en forma de un sólido de color amarillo. ^1H RMN (acetona– d_6): δ 8,98(dd, 1H), 8,88 (dd, 1H), 8,37 (d, 1H), 7,83 (dd, 1H), 7,49 (d, 1H), 7,27(dd, 1H), 6,66 (br s, 2H), 3,10–3,00 (m, 1H), 1,33 (d, 6H). LRMS [M + H] = 238,1.

Ejemplo 91.

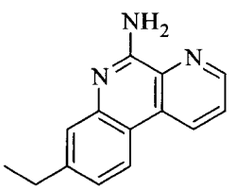
8–Vinilbenzo[f][1,7]naftiridin–5–amina.



A una solución de yoduro de metil trifenil fosfonio (6,0 eq.) se agregó *n*BuLi (7,0 eq.) a –78°C. La mezcla de reacción se dejó entibiar hasta 0°C y se agitó durante 30 minutos (color anaranjado oscuro). La reacción se enfrió nuevamente hasta –78°C, y se introdujo en la reacción, por goteo, 5–aminobenzo[f][1,7]naftiridina–8–carbaldehído (del Ejemplo 87) (1,0 eq.) en THF. La reacción se dejó entibiar hasta temperatura ambiente durante la noche. La reacción se apagó con NH_4Cl saturado y se extrajo con EtOAc. La capa orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío, de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–50% de EtOAc/Hexanos, a fin de lograr 8–vinilbenzo[f][1,7]naftiridin–5–amina como un sólido de color blanco. ^{1}H RMN (acetona– d_6): ^{1}H RMN (acetona– d_6): δ 9,00 (dd, 1H), 8,90 (dd, 1H), 8,41 (d, 1H), 7,84 (dd, 1H), 7,65 (d, 1H), 7,52(dd, 1H), 6,91 (dd, 1H), 6,77 (br s, 2H), 5,97 (dd, 1H), 5,34 (dd, 1H). LRMS [M + H] = 222,1.

Ejemplo 92.

8–Etilbenzo[f][1,7]naftiridin–5–amina.

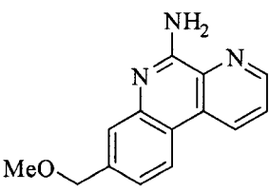


Una mezcla de 8–vinilbenzo[f][1,7]naftiridin–5–amina (1,0 eq.) (del Ejemplo 91) y Pd/C (húmedo, 10% en peso) en EtOH se agitó bajo un balón de H_2 durante la noche. La mezcla de reacción se diluyó con DCM. El Pd/C se separó mediante la filtración a través de celite, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El material bruto se purificó por medio de la

cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–60% de EtOAc/Hexanos, a fin de lograr 8–etilbenzo[f][1,7]naftiridin–5–amina en forma de una espuma de color blanco. ^{1}H RMN (acetona– d_6): δ 8,98(dd, 1H), 8,88 (dd, 1H), 8,35 (d, 1H), 7,82 (dd, 1H), 7,46 (d, 1H), 7,22(dd, 1H), 6,63 (br s, 2H), 2,78 (q, 2H), 1,30 (t, 3H). LRMS [M + H] = 224,1.

Ejemplo 93.

8–(Metoximetil)benzo[f][1,7]naftiridin–5–amina.



Etapa 1: ter–butil 2–cloro–5–(metoximetil)fenilcarbamato.

A una solución de 2–cloro–5–(metoximetil)anilina (comercial) (1,0 eq.) en THF (0,2 M) a 0°C en una atmósfera de N_2 se agregó, por goteo, NaHMDS, 1 M (2,5 eq.). La reacción se agitó durante 15 minutos a 0°C, y se agregó una solución de di–*ter*–butil dicarbonato. La reacción se entibió hasta temperatura ambiente durante la noche. Se evaporó el solvente, y el residuo resultante se apagó con solución acuosa de HCl, 0,1 N. La suspensión acuosa se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–30% de EtOAc/Hexanos, a fin de lograr ter–butil 2–cloro–5–(metoximetil)fenilcarbamato en forma de un aceite incoloro.

Etapa 2: ter–butil 5–(metoximetil)–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato.

Ter–butil 2–cloro–5–(metoximetil)fenilcarbamato (de la etapa previa) (1,0 eq.), 4,4,4',4',5,5,5',5'–octametil–2,2'–bi(1,3,2–dioxaborolano) (3,0 eq.), Pd_2dba_3 (2,5%), XPhos (10%) y COAc (3 eq.) se mezclaron en dioxano (0,2 M) en una atmósfera de N_2. La reacción se calentó hasta 110°C y se agitó durante la noche.

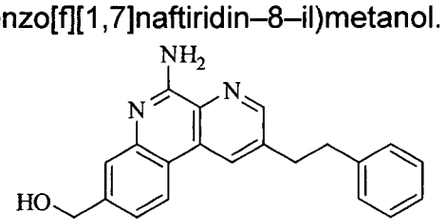
La suspensión resultante se enfrió hasta temperatura ambiente, se diluyó con éter, se filtró a través de celite, y el filtrado se concentró al vacío. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–20% de EtOAc/Hexanos, a fin de lograr ter–butil 5–(metoximetil)–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato en forma de una espuma de color blanco.

Etapa 3: 8–(metoximetil)benzo[f][1,7]naftiridin–5–amina.

Una solución de *ter*–butil 5–(metoximetil)–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (de la etapa previa) (1,0 eq.) y 3–bromopicolino–nitrilo (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con 2% de MeOH en DCM y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con 2% de MeOH en DCM. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–100% de EtOAc/Hexanos, a fin de lograr 8–(metoximetil)benzo[f][1,7]naftiridin–5–amina como un sólido de color blanco. ^1H RMN (metanol– d_4): δ 8,97(dd, 1H), 8,91 (dd, 1H), 8,41 (dd, 1H), 7,83 (dd, 1H), 7,59 (d, 1H), 7,37(dd, 1H), 4,62 (s, 2H), 3,45 (s, 3H). LRMS [M + H] = 240,1.

Ejemplo 94.

(5–Amino–2–fenetilbenzo[f][1,7]naftiridin–8–il)metanol.



Etapa 1: metil 5–amino–2–fenetilbenzo[f][1,7]naftiridina–8–carboxilato.

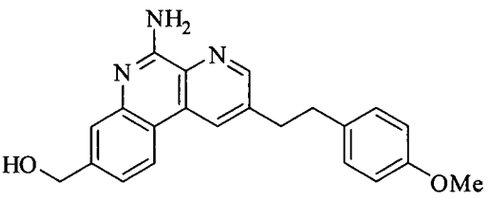
Una solución de ácido 2–(*ter*–butoxicarbonilamino)–4–(metoxicarbonil) fenilbórico (del Ejemplo 85/Etapa1) (1,0 eq.) y 2–cloro–6–fenetilnicotinonitrilo (preparado a partir de *(E)*–3–cloro–5–estirilpicolinonitrilo (del Ejemplo 32/Etapa 1) siguiendo el procedimiento descripto en el Ejemplo 114/Etapa 3) (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (2,0 eq.) en tolueno/etanol (2:1, 0,03 M) se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con EtOAc y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–60% de EtOAc/Hexanos, a fin de lograr metil 5–amino–2–fenetilbenzo[f][1,7]naftiridina–8–carboxilato como un sólido de color blanco.

Etapa 2: (5–amino–2–fenetilbenzo[f][1,7]naftiridin–8–il)metanol.

A una solución de metil 5–amino–2–fenetilbenzo[f][1,7]naftiridina–8–carboxilato (de la etapa previa) (1,0 eq.) en THF (0,03 M) se agregó Super–H (10 eq.) a 0°C. La solución se dejó entibiar hasta temperatura ambiente en un período de 30 min. La reacción se apagó con agua hasta que ya no hubo burbujeo. Se separaron las capas, y la capa acuosa se extrajo con EtOAc. La capa orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–10% de MeOH/DCM, a fin de lograr (5–amino–2–fenetilbenzo[f][1,7]naftiridin–8–il)metanol en forma de un sólido blanquecino. ^{1}H RMN (metanol– d_4): δ 8,63 (dd, 1H), 8,56 (dd, 1H), 8,24 (d, 1H), 7,57 (d, 1H), 7,35 (dd, 1H), 7,27–7,15 (m, 5H), 4,75 (s, 2H), 3,20 (t, 2H), 3,06 (t, 2H). LRMS [M + H] = 330,1.

Ejemplo 95.

(5–Amino–2–(4–metoxifenetil)benzo[f][1,7]naftiridin–8–il)metanol.



Etapa 1: metil 5–amino–2–(4–metoxifenetil)benzo[f][1,7]naftiridina–8–carboxilato.

Una solución de ácido 2–(*ter*–butoxicarbonilamino)–4–(metoxicarbonil) fenilbórico (del Ejemplo 85/Etapa1) (1,0 eq.) y 2–cloro–6–(4–metoxifenetil)nicotinonitrilo (preparado a partir de la reacción de 3,5–dicloropicolinonitrilo con 1–etinil–4–metoxibenceno, siguiendo el procedimiento descripto en el Ejemplo 44/Etapa 3, y la reducción del producto, siguiendo el procedimiento descripto en el Ejemplo 114/Etapa 3) (1,0 eq.)), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (2,0 eq.) en tolueno/etanol (2:1, 0,03 M) se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con EtOAc y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de EtOAc/Hexanos, a fin de lograr metil 5–amino–2–(4–metoxifenetil)benzo[f][1,7]naftiridina–8–carboxilato como un sólido de color blanco.

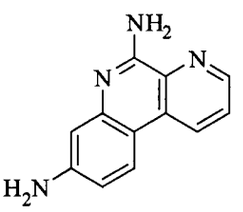
Etapa 2: (5–amino–2–(4–metoxifenetil)benzo[f][1,7]naftiridin–8–il)metanol.

A una solución de metil 5–amino–2–(4–metoxifenetil)benzo[f][1,7] naftiridina–8–carboxilato (de la etapa previa) (1,0 eq.) en THF (0,03 M) se agregó Super–H (10 eq.) a 0°C. La solución se dejó entibiar hasta temperatura ambiente

en un período de 30 minutos. La reacción se apagó con agua hasta que ya no hubo burbujeo. Se separaron las capas, y la capa acuosa se extrajo con EtOAc. La capa orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío, de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–100% de EtOAc/Hexanos, a fin de lograr (5–amino–2–(4–metoxifenetil)benzo[f][1,7]naftiridin–8–il)metanol en forma de un sólido blanquecino (31%). ^{1}H RMN (acetona– d_6): δ 8,79 (d, 1H), 8,70 (d, 1H), 8,35 (d, 1H), 7,61 (d, 1H), 7,33 (dd, 1H), 7,13 (d, 2H), 6,83 (d, 2H), 6,62 (br s, 2H), 4,47 (s, 2H), 4,40 (br s, 1H), 3,75 (s, 3H), 3,22 (t, 2H), 3,06 (t, 2H). LRMS [M + H] = 360,2.

Ejemplo 96.

Benzo[f][1,7]naftiridina–5,8–diamina.



Etapa 1: ter–butil 2–bromo–5–nitrofenilcarbamato.

A una solución de 2–bromo–5–nitroanilina (comercial) (1,0 eq.) en THF (0,2 M) a 0°C en una atmósfera de N_2 se agregó, por goteo, NaHMDS, 1 M (2,5 eq.). La reacción se agitó durante 15 minutos a 0°C, y se agregó una solución de di–*ter*–butil dicarbonato en THF. La reacción se entibió hasta temperatura ambiente durante la noche. Se evaporó el solvente, y el residuo resultante se apagó con solución acuosa de HCl, 0,1 N. La suspensión acuosa se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–30% de EtOAc/Hexanos, a fin de lograr ter–butil 2–bromo–5–nitrofenilcarbamato en forma de un aceite incoloro.

Etapa 2: ter–butil 5–nitro–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenil carbamato.

Ter–butil 2–bromo–5–nitrofenilcarbamato (de la etapa previa) (1,0 eq.), 4,4,4',4',5,5,5',5'–octametil–2,2'–bi(1,3,2–dioxaborolano) (1,8 eq.), dicloro[1,1'–bis(difenil fosfino)ferroceno]paladio (II) (5%) y acetato de sodio (4,5 eq.) se mezclaron en dioxano (0,2 M) en una atmósfera de N_2. La reacción se calentó hasta 100°C y se agitó durante la noche. La suspensión resultante se enfrió hasta temperatura ambiente, se diluyó con éter, se filtró a través de celite, y el filtrado se concentró al vacío. El residuo se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–30% de EtOAc/Hexanos, a fin de lograr ter–butil 5–nitro–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenil carbamato en forma de una espuma.

Etapa 3: 8–nitrobenzo[f][1,7]naftiridin–5–amina.

Una solución de *ter*–butil 5–nitro–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (de la etapa previa) (1,0 eq.) y 3–bromopicolinonitrilo (1,0 eq.) en tolueno (0,44 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se filtró de manera de recoger el precipitado. El precipitado se enjuagó con EtOAc a fin de lograr 8–nitrobenzo[f][1,7]naftiridin–5–amina en forma de un sólido de color amarillo.

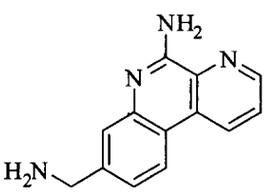
Etapa 4: benzo[f][1,7]naftiridina–5,8–diamina.

Una mezcla de 8–nitrobenzo[f][1,7]naftiridin–5–amina (de la etapa previa) (1,0 eq.) y Pd/C (húmedo, 10% en peso) en EtOH se agitó bajo un balón de H_2 durante la noche. La mezcla de reacción se diluyó con DCM. El sólido insoluble se separó mediante la filtración a través de celite, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El material bruto se lavó con acetona a fin

de lograr benzo[f][1,7]naftiridina–5,8–diamina en forma de un sólido blanquecino. ^{1}H RMN (metanol– d_4): δ 8,73 (dd, 1H), 8,71 (dd, 1H), 8,11 (d, 1H), 7,69 (dd, 1H), 6,86 (d, 1H), 6,82 (dd, 1H). LRMS [M + H] = 211,1.

Ejemplo 97.

8–(Aminometil)benzo[f][1,7]naftiridin–5–amina.



Etapa 1: ácido 2–(ter–butoxicarbonilamino)–4–cianofenilbórico.

El compuesto del enunciado se preparó de acuerdo con el procedimiento descripto en el Ejemplo 85/Etapa 1, pero usando clorhidrato de ácido 2–amino–4–cianofenilbórico (comercial) como el material inicial. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–30% de MeOH/DCM, a fin de lograr ácido 2–(ter–butoxicarbonilamino)–4–cianofenilbórico en forma de un sólido blanquecino.

Etapa 2: 5–aminobenzo[f][1,7]naftiridina–8–carbonitrilo.

El compuesto del enunciado se preparó de acuerdo con el procedimiento descripto en el Ejemplo 96/Etapa 3, pero usando ácido 2–(*ter*–butoxicarbonilamino)–4–cianofenilbórico (de la etapa previa) como el material inicial. El material bruto se enjuagó con 1:1 de EtOAc/Hexanos. a fin de lograr 5–aminobenzo[f][1,7]naftiridina–8–carbonitrilo en forma de un sólido de color amarillo pálido.

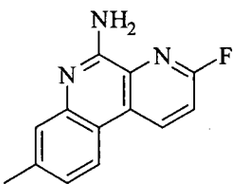
Etapa 4: benzo[f][1,7]naftiridina–5,8–diamina.

Una mezcla de 8–nitrobenzo[f][1,7]naftiridin–5–amina (de la etapa previa) (1,0 eq.) y níquel Raney (húmedo, 10% en peso) en EtOH/amoníaco (2:1) se agitó bajo un balón de H_2 durante la noche. La mezcla de reacción se diluyó con DCM. El sólido insoluble se separó por medio de la filtración a través de celite, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El material

bruto se lavó con 10% de MeOH/DCM y 70% de EtOAc/Hexanos, a fin de lograr benzo[f][1,7]naftiridina–5,8–diamina en forma de un sólido blanquecino. ^{1}H RMN (metanol– d_4): δ 8,97 (dd, 1H), 8,90 (dd, 1H), 8,41 (d, 1H), 7,83 (dd, 1H), 7,57 (d, 1H), 7,39 (dd, 1H), 3,96 (s, 2). LRMS [M + H] = 229,1.

Ejemplo 98.

3–Fluor–8–metilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 3–cloro–8–metilbenzo[f][1,7]naftiridin–5–amina.

Una solución de *ter*–butil 5–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (del Ejemplo 5/Etapa 2) (1,0 eq.) y 3–bromo–6–cloropicolinonitrilo (del Ejemplo 20/Etapa 2) (1,0 eq.), tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de sodio, 2 N (2,0 eq.) en tolueno/etanol (2:1, 0,03 M) se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con EtOAc y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–40% de EtOAc/Hexanos, a fin de lograr 3–cloro–8–metilbenzo[f][1,7]naftiridin–5–amina en forma de un sólido de color amarillo pálido.

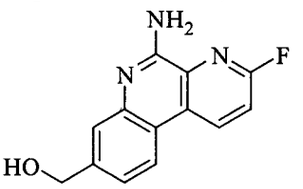
Etapa 2: 3–fluor–8–metilbenzo[f][1,7]naftiridin–5–amina.

Una mezcla de 3–cloro–8–metilbenzo[f][1,7]naftiridin–5–amina (de la etapa previa) (1,0 eq.) fluoruro de potasio (4,0 eq.) y 18–corona–6 (0,4 eq.) en NMP (0,1 M) se calentó en un reactor de microondas a 210°C durante 2 horas. Después de enfriar hasta temperatura ambiente, el residuo de la reacción se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–

30% de EtOAc/Hexanos, a fin de lograr 3–fluor–8–metilbenzo[f][1,7]naftiridin–5–amina como un sólido de color blanco. ^{1}H RMN (acetona– d_6): δ 9,20 (dd, 1H), 8,32 (d, 1H), 7,58 (dd, 1H), 7,46 (d, 1H), 7,21 (dd, 1H), 6,51 (br s, 2H), 2,47 (s, 3H). LRMS [M + H] = 228,1.

Ejemplo 99 .

(5–Amino–3–fluorbenzo[f][1,7]naftiridin–8–il)metanol.



Etapa 1: ter–butil 5–((ter–butildimetilsililoxi)metil)–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato.

El compuesto del enunciado se preparó de acuerdo con el procedimiento descripto en el Ejemplo 93/Etapas 1 y 2, pero usando 5–((*ter*–butildimetilsililoxi)metil)–2–cloroanilina (comercial) como el material inicial. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–20% de EtOAc/Hexanos, a fin de lograr ter–butil 5–((ter–butildimetilsililoxi)metil)–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato en forma de una espuma de color blanco.

Etapa 2: 8–((ter–butildimetilsililoxi)metil)–3–clorobenzo[f][1,7]naftiridin–5–amina.

El compuesto del enunciado se preparó de acuerdo con el procedimiento descripto en el Ejemplo 98/Etapa 1, pero usando *ter*–butil 5–((*ter*–butildimetilsililoxi)metil)–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (de la etapa previa) como el material inicial. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–15% de EtOAc/Hexanos, a fin de lograr 8–((ter–butildimetilsililoxi)metil)–3–clorobenzo[f][1,7]naftiridin–5–amina en forma de un sólido de color amarillo pálido.

Etapa 3: (5–amino–3–clorobenzo[f][1,7]naftiridin–8–il)metanol.

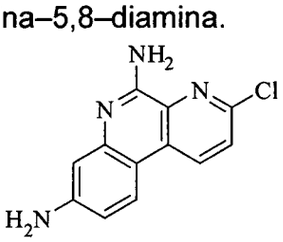
Una solución de 8–((*ter*–butildimetilsililoxi)metil)–3–clorobenzo[f][1,7] naftiridin–5–amina (de la etapa previa) (1,0 eq.) y TBAF (1,1 eq.) en THF se agitó a temperatura ambiente durante la noche. La reacción se apagó con $NaHCO_3$ saturado. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con Et_2O. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de MeOH/DCM, a fin de lograr (5–amino–3–clorobenzo[f][1,7]naftiridin–8–il)metanol como un sólido de color blanco.

Etapa 4: (5–amino–3–fluorbenzo[f][1,7]naftiridin–8–il)metanol.

El compuesto del enunciado se preparó de acuerdo con el procedimiento descripto en el Ejemplo 98/Etapa 2, pero usando (5–amino–3–clorobenzo[f][1,7]naftiridin–8–il)metanol (de la etapa previa) como el material inicial. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–40% de EtOAc/Hexanos, a fin de lograr (5–amino–3–fluorbenzo[f][1,7]naftiridin–8–il)metanol como un sólido de color blanco. ^{1}H RMN (metanol– d_4): δ 9,15 (dd, 1H), 8,38 (d, 1H), 7,64 (d, 1H), 7,55 (dd, 1H), 7,41 (dd, 1H), 4,77 (s, 2H). LRMS [M + H] = 244,1.

Ejemplo 100.

3–Clorobenzo[f][1,7]naftiridina–5,8–diamina.



Etapa 1: 3–cloro–8–nitrobenzo[f][1,7]naftiridin–5–amina.

El compuesto del enunciado se preparó de acuerdo con el procedimiento descripto en el Ejemplo 98/Etapa 1, pero usando *ter*–butil 5–nitro–2–(4,4,5,5–

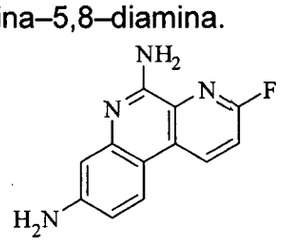
tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (comercial) como el material inicial. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–40% de EtOAc/Hexanos, a fin de lograr 3–cloro–8–nitrobenzo[f][1,7]naftiridin–5–amina en forma de un sólido de color amarillo pálido.

Etapa 2: 3–clorobenzo[f][1,7]naftiridina–5,8–diamina.

Una mezcla de 8–nitrobenzo[f][1,7]naftiridin–5–amina (de la etapa previa) (1,0 eq.) y níquel Raney (húmedo, 10% en peso) en EtOH se agitó bajo un balón de H_2 durante la noche. La mezcla de reacción se diluyó con DCM. El sólido insoluble se separó por medio de la filtración a través de celite, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–100% de EtOAc/Hexanos, a fin de lograr 3–clorobenzo[f][1,7]naftiridina–5,8–diamina como un sólido de color blanco. ^{1}H RMN (metanol– d_4): δ 8,75 (d, 1H), 8,08 (dd, 1H), 7,70 (d, 1H), 6,84–6,81 (m, 2H). LRMS [M + H] = 245,1.

Ejemplo 101.

3–Fluorbenzo[f][1,7]naftiridina–5,8–diamina.

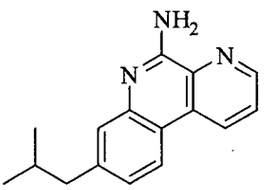


El compuesto del enunciado se preparó de acuerdo con el procedimiento descripto en el Ejemplo 98/Etapa 2, pero usando 3–clorobenzo[f][1,7]naftiridina–5,8–diamina (del Ejemplo 100) como el material inicial. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–7% de MeOH/DCM, a fin de lograr 3–fluorbenzo[f][1,7]naftiridina–5,8–diamina como un sólido de color blanco. ^{1}H RMN

(metanol– d_4): δ 8,93 (dd, 1H), 8,09 (d, 1H), 7,44 (dd, 1H), 6,86–6,83 (m, 2H). LRMS [M + H] = 229,1.

Ejemplo 102.

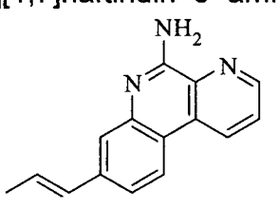
8–Isobutilbenzo[f][1,7]naftiridin–5–amina.



Se preparó 8–isobutilbenzo[f][1,7]naftiridin–5–amina a partir de 5–aminobenzo[f][1,7]naftiridina–8–carbaldehído (del Ejemplo 87) con bromuro de isopropil(trifenil)fosfonio, siguiendo los procedimientos descriptos para el Ejemplo 91 (reacción de Wittig) y el Ejemplo 92 (reducción). ^{1}H RMN (acetona– d_6): δ 8,98(dd, 1H), 8,88 (dd, 1H), 8,35 (d, 1H), 7,82 (dd, 1H), 7,44 (d, 1H), 7,18 (dd, 1H), 6,73 (br s, 2H), 2,63 (d, 2H), 2,04–1,94 (m, 1H), 0,94 (d, 6H). LRMS [M + H] = 252,1.

Ejemplo 103.

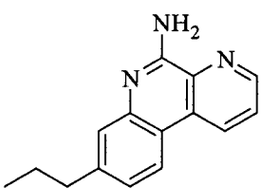
(*E*)–8–(Prop–1–enil)benzo[f][1,7]naftiridin–5–amina.



Se preparó (*E*)–8–(prop–1–enil)benzo[f][1,7]naftiridin–5–amina a partir de 5–aminobenzo[f][1,7]naftiridina–8–carbaldehído (del Ejemplo 87) con bromuro de etil(trifenil)fosfonio, siguiendo los procedimientos descriptos para el Ejemplo 91. ^{1}H RMN (acetona– d_6): δ 8,98 (dd, 1H), 8,88 (dd, 1H), 8,36 (d, 1H), 7,83 (dd, 1H), 7,54 (d, 1H), 7,43 (dd, 1H), 6,67 (br s, 2H), 6,60–6,42 (m, 2H), 1,92 (dd, 3H). LRMS [M + H] = 236,1.

Ejemplo 104.

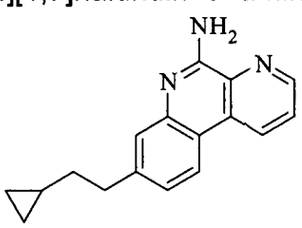
8–Propilbenzo[f][1,7]naftiridin–5–amina.



Se preparó 8–propilbenzo[f][1,7]naftiridin–5–amina a partir de (*E*)–8–(prop–1–enil)benzo[f][1,7]naftiridin–5–amina (del Ejemplo 103), siguiendo los procedimientos descriptos para el Ejemplo 92. ^{1}H RMN (acetona– d_6): δ 8,99 (dd, 1H), 8,88 (dd, 1H), 8,35 (d, 1H), 7,83 (dd, 1H), 7,45 (d, 1H), 7,21 (dd, 1H), 6,64 (br s, 2H), 2,74 (t, 2H), 1,74 (qt, 2H), 0,98 (t, 3H). LRMS [M + H] = 238,1.

Ejemplo 105.

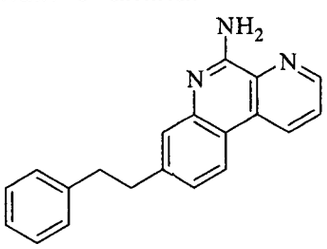
8–(2–Ciclopropiletil)benzo[f][1,7]naftiridin–5–amina.



Se preparó 8–(2–ciclopropiletil)benzo[f][1,7]naftiridin–5–amina a partir de 5–aminobenzo[f][1,7]naftiridina–8–carbaldehído (del Ejemplo 87) con bromuro de (ciclopropilmetil)trifenilfosfonio, siguiendo los procedimientos descriptos para el Ejemplo 91 (reacción de Wittig) y el Ejemplo 92 (reducción). ^{1}H RMN (acetona–d_6): δ 8,99 (dd, 1H), 8,88 (dd, 1H), 8,35 (d, 1H), 7,83 (dd, 1H), 7,47 (d, 1H), 7,23 (dd, 1H), 6,64 (br s, 2H), 1,60 (q, 2H), 1,34–1,25 (m, 1H), 0,91–0,72 (m, 2H), 0,45–0,41 (m, 2H), 0,11–0,07 (m, 2H). LRMS [M + H] = 264,1.

Ejemplo 106.

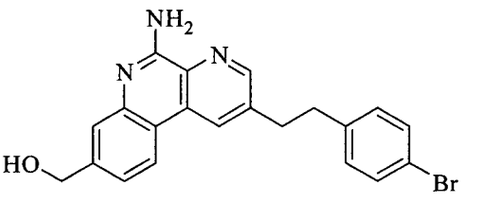
8–Fenetilbenzo[f][1,7]naftiridin–5–amina.



Se preparó 8–fenetilbenzo[f][1,7]naftiridin–5–amina a partir de 5–aminobenzo[f][1,7]naftiridina–8–carbaldehído (del Ejemplo 87) con bromuro de benciltrifenilfosfonio, siguiendo los procedimientos descriptos para el Ejemplo 91 (reacción de Wittig) y el Ejemplo 92 (reducción). ^{1}H RMN (acetona– d_6): δ 8,99 (dd, 1H), 8,88 (dd, 1H), 8,35 (d, 1H), 7,83 (dd, 1H), 7,49 (d, 1H), 7,29–7,15 (dd, 6H), 6,70 (br s, 2H), 3,10–3,00 (m, 4H). LRMS [M + H] = 300,1.

Ejemplo 107.

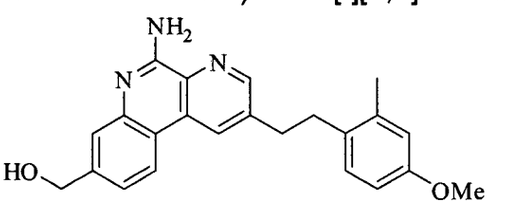
(5–Amino–2–(4–bromofenetil)benzo[f][1,7]naftiridin–8–il)metanol.



Se preparó (5–amino–2–(4–bromofenetil)benzo[f][1,7]naftiridin–8–il)metanol a partir de (5–amino–2–(4–metoxifenetil)benzo[f][1,7]naftiridin–8–il)metanol (del Ejemplo 95), siguiendo los procedimientos descriptos para el Ejemplo 86. ^{1}H RMN (acetona– d_6): δ 8,81 (d, 1H), 8,72 (d, 1H), 8,40 (d, 1H), 7,68 (d, 1H), 7,39 (dd, 1H), 7,08 (d, 2H), 6,74 (d, 2H), 6,66 (br s, 2H), 4,49 (s, 2H), 3,21 (t, 2H), 3,03 (t, 2H). LRMS [M + H] = 408,1.

Ejemplo 108.

(5–Amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)metanol.

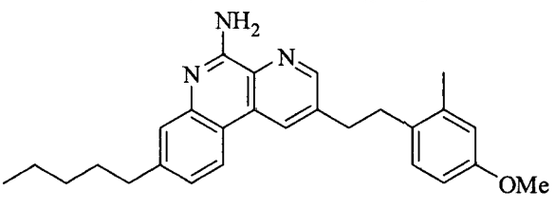


Se preparó (5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)metanol a partir de ter–butil 5–((ter–butildimetilsililoxi)metil)–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (Ejemplo 99/Etapa 1) y 3–cloro–5–((4–metoxi–2–metilfenil)etinil)picolinonitrilo (del Ejemplo 49/Etapa 1), siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 4 y la

desprotección del grupo TBS, siguiendo el procedimiento que se describe en el Ejemplo 99/Etapa 3. ^{1}H RMN (acetona– d_6): δ 8,79 (s, 1H), 8,73 (s, 1H), 8,35 (d, 1H), 7,61 (s, 1H), 7,33 (d, 1H), 7,09 (d, 1H), 6,75 (d, 1H), 6,68 (dd, 1H), 6,57 (br s, 2H), 4,47 (d, 2H), 4,32 (t, 1H), 3,58 (s, 3H), 3,17 (t, 2H), 3,04 (t, 2H), 2,30 (s, 3H). LRMS [M + H] = 374,2.

Ejemplo 109

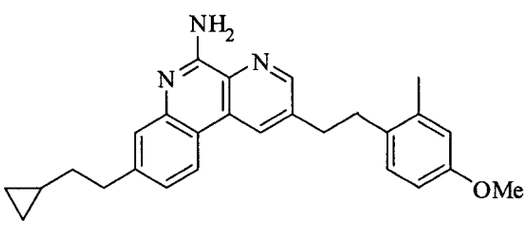
2–(4–Metoxi–2–metilfenetil)–8–pentilbenzo[f][1,7]naftiridin–5–amina



y

Ejemplo 110

8–(2–Ciclopropiletil)–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–5–amina.



Etapa 1: ter–butil 5–bromo–2–clorofenilcarbamato.

El compuesto del enunciado se preparó de acuerdo con el procedimiento descripto en el Ejemplo 5/Etapa 1, pero usando 5–bromo–2–cloroanilina (comercial) como el material inicial. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–40% de EtOAc/Hexanos, a fin de lograr ter–butil 5–bromo–2–clorofenilcarbamato en forma de un sólido de color amarillo pálido.

Etapa 2: (E)–ter–butil 2–cloro–5–(2–ciclopropilvinil)fenilcarbamato.

Una solución de *ter*–butil 5–bromo–2–clorofenilcarbamato (de la etapa previa) (1,0 eq.) y (*E*)–2–(2–ciclopropilvinil)–4,4,5,5–tetrametil–1,3,2–

dioxaborolano (comercial) (1,0 eq.) en tolueno (0,2 M) se mezcló con tetraquis(trifenil–fosfina)paladio (5% en moles) y solución acuosa de carbonato de potasio, 2 N (2,0 eq.). La reacción se calentó hasta 100°C y se agitó durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con EtOAc y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–5% de EtOAc/Hexanos, a fin de lograr (E)–ter–butil 2–cloro–5–(2–ciclopropilvinil)fenilcarbamato en forma de un sólido de color amarillo pálido.

Etapa 3: (E)–ter–butil 5–(2–ciclopropilvinil)–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato.

El compuesto del enunciado se preparó de acuerdo con el procedimiento descripto en el Ejemplo 93/Etapa 2, pero usando *(E)–ter*–butil 2–cloro–5–(2–ciclopropilvinil) fenilcarbamato (de la etapa previa) como el material inicial. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–10% de EtOAc/Hexanos, a fin de lograr (E)–ter–butil 5–(2–ciclopropilvinil)–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato en forma de un sólido de color amarillo pálido.

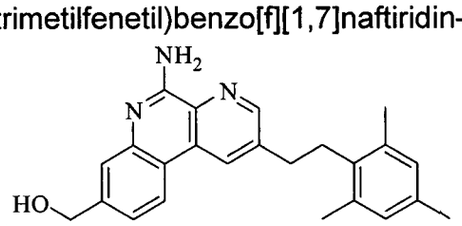
Etapa 4: 2–(4–metoxi–2–metilfenetil)–8–pentilbenzo[f][1,7]naftiridin–5–amina y 8–(2–ciclopropiletil)–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–5–amina.

Los compuestos del enunciado se prepararon de acuerdo con el procedimiento que se describe en el Ejemplo 44/Etapas 4 (acoplamiento de Suzuki) y 5 (reducción), pero usando *(E)–ter*–butil 5–(2–ciclopropilvinil)–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (de la etapa previa) y 3–cloro–5–((4–metoxi–2–metilfenil)etinil) picolinonitrilo (del Ejemplo 49/Etapa 1)

como el material inicial. El producto bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–40% de EtOAc/Hexanos, a fin de lograr el Ejemplo 109 como un sólido de color blanco: ^{1}H RMN (acetona– d_6): δ 8,76 (d, 1H), 8,70 (d, 1H), 8,29 (d, 1H), 7,44 (d, 1H), 7,18 (dd, 1H), 7,08 (d, 1H), 6,74 (d, 1H), 6,68 (dd, 1H), 6,59 (br s, 2H), 3,74 (s, 3H), 3,18 (t, 2H), 3,04 (t, 2H), 2,75 (t, 2H), 2,29 (s, 3H), 1,75–1,68 (m, 2H), 1,40–1,35 (m, 4H), 0,90 (s, 3H); LRMS [M + H] = 414,3; y el Ejemplo 110 en forma de un sólido blanquecino: ^{1}H RMN (acetona– d_6): δ 8,76 (d, 1H), 8,70 (d, 1H), 8,28 (d, 1H), 7,45 (d, 1H), 7,19 (dd, 1H), 7,08 (d, 1H), 6,74 (d, 1H), 6,67 (dd, 1H), 6,55 (br s, 2H), 3,73 (s, 3H), 3,16 (t, 2H), 3,03 (t, 2H), 2,29 (s, 3H), 1,60 (q, 2H), 1,29–1,28 (m, 1H), 0,89–0,74 (m, 2H), 0,44–0,41 (m, 2H), 0,10–0,07 (m, 2H); LRMS [M + H] = 412,3.

Ejemplo 111.

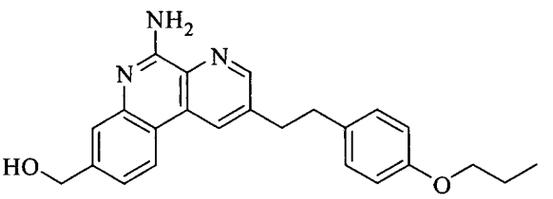
(5–Amino–2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–8–il)metanol.



Se preparó (5–amino–2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–8–il)metanol a partir de *ter*–butil 5–((*ter*–butildimetilsililoxi)metil)–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (del Ejemplo 99/etapa 1), 2–etinil–1,3,5–trimetilbenceno (comercial) y 3–cloro–5–(mesitiletinil)picolinonitrilo (del Ejemplo 77/etapa 1), siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 4, Ejemplo 99/etapa 3 (desprotección de TBS) y Ejemplo 77/etapa 3 (reducción). ^{1}H RMN (acetona– d_6): δ 8,77 (s, 2H), 8,34 (d, 1H), 7,61 (s, 1H), 7,33 (d, 1H), 6,84 (s, 2H), 6,60 (br s, 2H), 4,77 (d, 2H), 4,35 (t, 1H), 3,08 (s, 3H), 2,84 (s, 6H), 2,30–2,29 (m, 4H). LRMS [M + H] = 372,2.

Ejemplo 112.

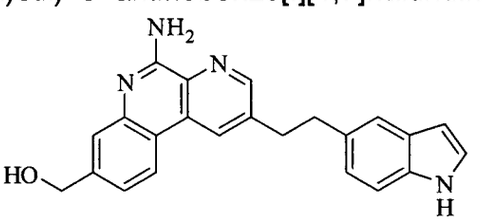
(5–Amino–2–(4–propoxifenetil)benzo[f][1,7]naftiridin–8–il)metanol.



Se preparó (5–amino–2–(4–propoxifenetil)benzo[f][1,7]naftiridin–8–il)metanol a partir de 8–((*ter*–butildimetilsililoxi)metil)–3–clorobenzo[f][1,7] naftiridin–5–amina (del Ejemplo 99/etapa 1) y 3–cloro–5–(4–propoxifenetil) picolinonitrilo (del Ejemplo 79/etapa 2), siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 4 y el Ejemplo 99/etapa 3 (desprotección de TBS). ^{1}H RMN (acetona– d_6): δ 8,79 (d, 1H), 8,70 (d, 1H), 8,35 (d, 1H), 7,61 (d, 1H), 7,33 (dd, 1H), 7,17 (d, 2H), 6,83 (d, 2H), 6,57 (br s, 2H), 4,77 (d, 2H), 4,34 (t, 1H), 3,89 (t, 2H), 3,22 (t, 2H), 3,06 (t, 2H), 1,83–1,70 (m, 2H), 1,00 (t, 3H). LRMS [M + H] = 388,2.

Ejemplo 113.

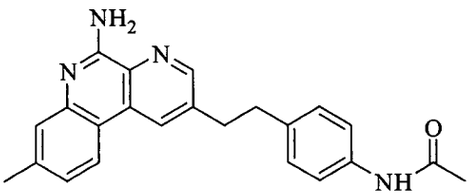
(2–(2–(1H–Indol–5–il)etil)–5–aminobenzo[f][1,7]naftiridin–8–il)metanol.



Se preparó (2–(2–(1H–indol–5–il)etil)–5–aminobenzo[f][1,7]naftiridin–8–il)metanol a partir de *ter*–butil 5–((*ter*–butildimetilsililoxi)metil)–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (del Ejemplo 99/etapa 1) y 5–((1H–indol–5–il)etinil)–3–cloropicolinonitrilo (del Ejemplo 44/etapa 3), siguiendo los procedimientos descriptos para el Ejemplo 44/Etapa 4 y el Ejemplo 99/etapa 3 (desprotección de TBS). ^{1}H RMN (acetona– d_6): δ 10,19 (t, 1H), 8,83 (d, 1H), 8,71 (d, 1H), 8,35 (d, 1H), 7,60 (d, 1H), 7,46 (d, 1H), 7,36–7,27 (m, 3H), 7,04 (dd, 1H), 6,57 (br s, 2H), 6,38 (dt, 1H), 4,77 (d, 2H), 4,36 (t, 1H), 3,29 (t, 2H), 3,19 (t, 2H). LRMS [M + H] = 369,2.

Ejemplo 114.

N–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)acetamida.



Etapa 1: N–(4–etinilfenil)acetamida.

A una solución de 4–etinilanilina (comercial) (1,0 eq.) y trietilamina (1,0 eq.) en cloruro de metileno (0,04 M), se agregó lentamente cloruro de acetilo (1,5 eq.). A continuación, la mezcla de reacción se agitó a 0°C durante 1 hora. Después de entibiar hasta temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr N–(4–etinilfenil)acetamida como un sólido de color blanco.

Etapa 2: N–(4–((5–cloro–6–cianopiridin–3–il)etinil)fenil)acetamida.

Una solución de 3,5–dicloropicolinonitrilo (1,0 eq.), N–(4–etinilfenil)acetamida (de la etapa previa) (1,0 eq.), cloruro de bis(trifenil–fosfina)paladio (10% en moles), yoduro de cobre (10% en moles) y trietilamina (5,0 eq.) en DMF (0,04 M) se agitó a 60°C durante 4 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases. La capa orgánica se lavó dos veces con agua, se secó sobre $MgSO_4$ anhidro y se concentró al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr N–(4–((5–cloro–6–cianopiridin–3–il)etinil)fenil)acetamida como un sólido de color blanco.

Etapa 3: N–(4–(2–(5–cloro–6–cianopiridin–3–il)etil)fenil)acetamida.

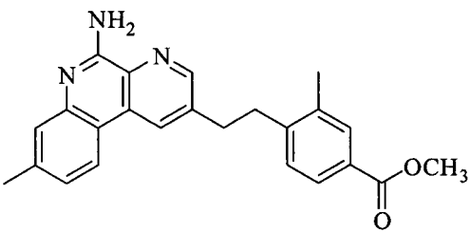
A una solución de N–(4–((5–cloro–6–cianopiridin–3–il)etinil)fenil)acetamida (de la etapa previa) en acetato de etilo/metanol (1:4, 0,05 M) se agregó 10% en peso de paladio sobre carbón (0,2 eq.). Se introdujo gas hidrógeno por medio de un balón, y la reacción se agitó durante 3 horas. La mezcla se filtró a través de una almohadilla de celite, lavando con diclorometano. El filtrado se concentró al vacío y se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr N–(4–(2–(5–cloro–6–cianopiridin–3–il)etil)fenil)acetamida.

Etapa 4: N–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)acetamida.

Una solución de N–(4–(2–(5–cloro–6–cianopiridin–3–il)etil)fenil)acetamida (de la etapa previa) (1,0 eq.), ter–butil 4–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (del Ejemplo 5/Etapa 2) (1,5 eq.), Tris(dibencilidenoacetona)dipaladio(0) (10% en moles), diciclohexil(2',6'–dimetoxibifenil–2–il)fosfina (20% en moles) y fosfato de potasio (2,0 eq.) en n–butanol/H_2O (2,5:1, 0,04 M) se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr N–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)acetamida como un sólido de color blanco. ^{1}H RMN ($CDCl_3$): δ 8,51 (s, 1H), 8,32 (s, 1H), 8,01 (d, 1H), 7,44 (s, 1H), 7,33–7,36 (m, 2H), 7,03–7,19 (m, 3H), 5,98 (br, 2H), 3,07–3,11 (m, 2H), 2,94–2,98 (m, 2H), 2,44 (s, 3H), 2,10 (s, 3H). LRMS [M + H] = 371,2.

Ejemplo 115.

Metil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato.



Etapa 1: metil 3–metil–4–((trietilsilil)etinil)benzoato.

Una solución de metil 4–bromo–3–metilbenzoato (1,0 eq.), trietil(etinil)silano (1,0 eq.), cloruro de bis(trifenil–fosfina)paladio (10% en moles), yoduro de cobre (10% en moles) y trietilamina (5,0 eq.) en DMF (0,04 M) se agitó a 60°C durante 4 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases. La capa orgánica se lavó dos veces con agua, se secó sobre $MgSO_4$ anhidro y se concentró al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–50% de acetato de etilo en hexano, a fin de lograr metil 3–metil–4–((trietilsilil)etinil)benzoato como un sólido de color blanco.

Etapa 2: metil 4–etinil–3–metilbenzoato.

A una solución de metil 3–metil–4–((trietilsilil)etinil)benzoato (de la etapa previa) (1,0 eq.) en THF (0,2 M), se agregó TBAF (0,2 eq.) lentamente a 0°C. A continuación, la mezcla de reacción se agitó a 0°C durante 1 hora. Después de entibiar hasta temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$, y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de

lograr metil 4–etinil–3–metilbenzoato como un sólido de color blanco.

Etapa 3: metil 4–((5–cloro–6–cianopiridin–3–il)etinil)–3–metilbenzoato.

Una solución de 3,5–dicloropicolinonitrilo (1,0 eq.), metil 4–etinil–3–metilbenzoato (de la etapa previa) (1,0 eq.), cloruro de bis(trifenil–fosfina)paladio (10 % en moles), yoduro de cobre (10% en moles) y trietilamina (5,0 eq.) en DMF (0,04 M) se agitó a 60°C durante 4 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases. La capa orgánica se lavó dos veces con agua, se secó sobre $MgSO_4$ anhidro y se concentró al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr metil 4–((5–cloro–6–cianopiridin–3–il)etinil)–3–metilbenzoato como un sólido de color blanco.

Etapa 4: metil metil 4–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)–3–metilbenzoato.

Una solución de metil 4–((5–cloro–6–cianopiridin–3–il)etinil)–3–metilbenzoato (de la etapa previa) (1,0 eq.), ter–butil 4–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (del Ejemplo 5/Etapa 2) (1,5 eq.), tris(dibencilidenoacetona)dipaladio(0) (10% en moles), diciclohexil(2',6'–dimetoxibifenil–2–il)fosfina (20% en moles) y fosfato de potasio (2,0 eq.) en n–butanol /H_2O (2,5:1, 0,04 M) se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr metil metil–4–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)–3–

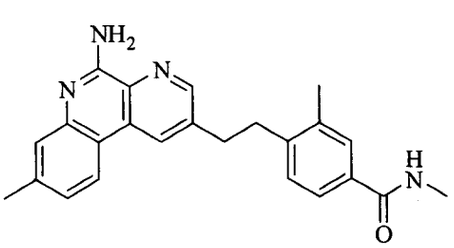
metilbenzoato como un sólido de color blanco.

Etapa 5: metil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato.

A una solución de metil metil 4–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)–3–metilbenzoato (de la etapa previa) en acetato de etilo/metanol (1:4, 0,05 M) se agregó 10% en peso de paladio sobre carbón (0,2 eq.). Se introdujo gas hidrógeno por medio de un balón, y la reacción se agitó durante 3 horas. La mezcla se filtró a través de una almohadilla de celite, lavando con diclorometano. El filtrado se concentró al vacío y se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr metil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato. ^{1}H RMN ($CDCl_3$): δ 8,61 (s, 1H), 8,40 (s, 1H), 8,09 (d, 1H), 7,83 (s, 1H), 7,81 (d, 1H), 7,54 (s, 1H), 7,18–7,20 (m, 2H), 6,17 (br, 2H), 3,92 (s, 3H), 3,10–3,16 (m, 4H), 2,53 (s, 3H), 2,36 (s, 3H). LRMS [M + H] = 386,2.

Ejemplo 116.

4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N,3–dimetilbenzamida.



Etapa 1: ácido 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoico.

Una solución de metil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato (del Ejemplo 115) (1,0 eq.) e hidróxido de sodio, 1 N (1,5 eq.) en metanol (0,04 M) se agitó a 60°C durante 4 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases. La capa orgánica se lavó dos veces con

agua, se secó sobre $MgSO_4$ anhidro y se concentró al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–50% de acetato de etilo en hexano, a fin de lograr ácido 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoico como un sólido de color blanco.

Etapa 2: cloruro de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoílo.

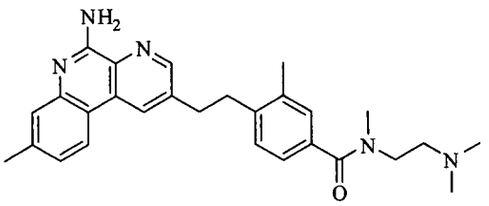
Una solución de ácido 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoico (de la etapa previa) en cloruro de tionilo se agitó a 60°C durante 3 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se concentró al vacío. El material bruto se usó para la siguiente etapa sin purificación.

Etapa 3: 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N,3–dimetilbenzamida.

A una solución de cloruro de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoílo (de la etapa previa) (Ejemplo 5) y trietilamina (2,5 eq.) en éter (0,05 M) se agregó metanamina (5,0 eq.). La mezcla de reacción se agitó durante la noche. A continuación, la mezcla de reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N,3–dimetilbenzamida como un sólido de color blanco. ^1H RMN ($CDCl_3$): δ 8,62 (s, 1H), 8,32 (s, 1H), 8,04 (d, 1H), 7,60 (s, 1H), 7,46–7,52 (m, 2H), 7,09–7,11 (m, 2H), 6,05 (br, 2H), 3,09–3,17 (m, 4H), 3,00 (d, 3H), 2,52 (s, 3H), 2,33 (s, 3H). LRMS [M + H] = 385,2.

Ejemplo 117.

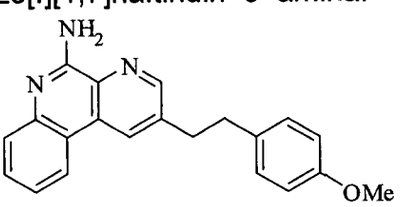
4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N,3–dimetilbenzamida.



A una solución de cloruro de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoílo (Ejemplo 116/Etapa 2) y trietilamina (2,5 eq.) en éter (0,05 M) se agregó N^1,N^1,N^2–trimetiletano–1,2–diamina (5,0 eq.). La mezcla de reacción se agitó durante la noche. A continuación, la mezcla de reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N,3–dimetilbenzamida como un sólido de color blanco. ^{1}H RMN ($CDCl_3$): δ 8,66 (s, 1H), 8,37 (s, 1H), 8,07 (d, 1H), 7,63 (s, 1H), 7,09–7,30 (m, 4H), 3,90 (br, 2H), 3,01–3,19 (m, 4H), 3,08 (s, 6H), 2,72 (br, 5H), 2,52 (s, 3H), 2,33 (s, 3H). LRMS [M + H] = 456,3.

Ejemplo 118.

2–(4–Metoxifenetil)benzo[f][1,7]naftiridin–5–amina.

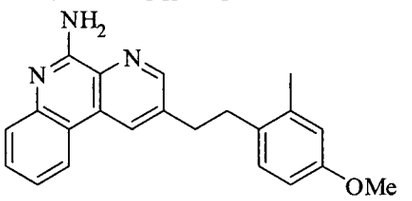


Se preparó 2–(4–metoxifenetil)benzo[f][1,7]naftiridin–5–amina a partir de 1–etinil–4–metoxibenceno (Ejemplo 116/Etapa 2) siguiendo los procedimientos

descriptos para el Ejemplo 45/Etapas 1 a 3. ^{1}H RMN ($CDCl_3$): δ 8,69 (s, 1H), 8,47 (s, 1H), 8,27 (d, 1H), 7,80 (d, 2H), 7,58–7,66 (m, 1H), 7,33–7,42 (m, 1H), 7,15 (d, 2H), 6,90 (d, 2H), 6,25 (br, 2H), 3,86 (s, 3H), 3,13–3,23 (m, 2H), 2,97–3,10 (m, 2H). LRMS [M + H] = 330,2.

Ejemplo 119.

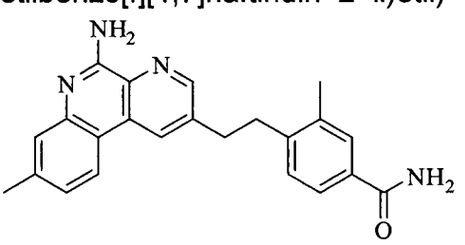
2–(4–Metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–5–amina.



Se preparó 2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–5–amina a partir de 1–etinil–4–metoxi–2–metilbenceno (comercial) siguiendo los procedimientos descriptos para el Ejemplo 45/Etapas 1 a 3. 1H RMN ($CDCl_3$): δ 8,60 (s, 1H), 8,37 (s, 1H), 8,18 (d, 1H), 7,69 (d, 1H), 7,49–7,57 (m, 1H), 7,24–7,34 (m, 1H), 6,98 (d, 1H), 6,56–6,70 (m, 2H), 6,00 (br, 2H), 3,70 (s, 3H), 3,00–3,09 (m, 2H), 2,83–2,96 (m, 2H), 2,20 (s, 3H). LRMS [M + H] = 344,2.

Ejemplo 120.

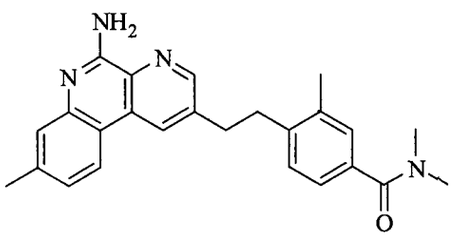
4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamida.



Se preparó 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamida a partir de cloruro de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoílo (Ejemplo 116/Etapa 2) y amoníaco, siguiendo los procedimientos descriptos para el Ejemplo 117. ^{1}H RMN ($CDCl_3$): δ 8,60 (s, 1H), 8,35 (s, 1H), 8,05 (d, 1H), 7,65 (s, 1H), 7,51–7,53 (m, 2H), 7,13–7,21 (m, 2H), 3,09–3,16 (m, 4H), 2,51 (s, 3H), 2,34 (s, 3H). LRMS [M + H] = 371,2.

Ejemplo 121.

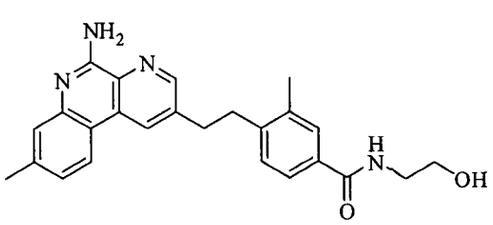
4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N,N,3–trimetilbenzamida.



Se preparó 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N,N,3–trimetilbenzamida a partir de cloruro de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoílo (Ejemplo 116/Etapa 2) y dimetilamina, siguiendo los procedimientos descriptos para el Ejemplo 117. ^{1}H RMN ($CDCl_3$): δ 8,68 (s, 1H), 8,32 (s, 1H), 8,04 (d, 1H), 7,66 (s, 1H), 7,31 (d, 1H), 7,06–7,18 (m, 3H), 3,08–3,19 (m, 4H), 2,96 (d, 3H), 2,54 (s, 3H), 2,33 (s, 3H), 2,05 (s, 3H). LRMS [M + H] = 399,2.

Ejemplo 122.

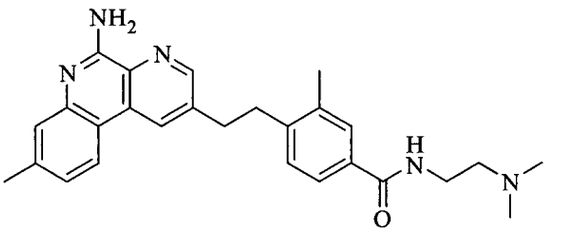
4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–hidroxietil)–3–metilbenzamida.



Se preparó 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–hidroxietil)–3–metilbenzamida a partir de cloruro de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoílo (Ejemplo 116/Etapa 2) y 2–aminoetanol, siguiendo los procedimientos descriptos para el Ejemplo 117. ^{1}H RMN ($CDCl_3$): δ 8,59 (s, 1H), 8,34 (s, 1H), 8,04 (d, 1H), 7,50–7,62 (m, 3H), 7,08–7,25 (m, 2H), 3,80 (t, 2H), 3,63 (t, 2H), 3,07–3,16 (m, 4H), 2,51 (s, 3H), 2,32 (s, 3H). LRMS [M + H] = 415,2.

Ejemplo 123.

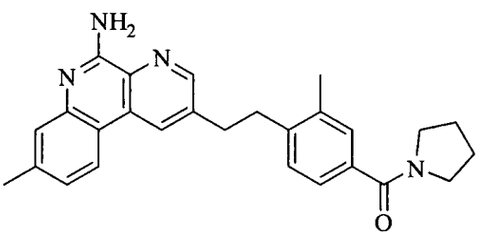
4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–3–metilbenzamida.



Se preparó 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–3–metilbenzamida a partir de cloruro de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoílo (Ejemplo 116/Etapa 2) y N^1,N^1–dimetiletano–1,2–diamina, siguiendo los procedimientos descriptos para el Ejemplo 117. ^{1}H RMN (metanol– d_4): δ 8,60 (s, 1H), 8,39 (s, 1H), 8,08 (d, 1H), 7,68 (s, 1H), 7,57–7,59 (m, 2H), 7,19–7,22 (m, 2H), 3,57–3,61 (m, 2H), 3,07–3,16 (m, 4H), 2,64–2,67 (m, 2H), 2,52 (s, 3H), 2,38 (s, 6H), 2,35 (s, 3H). LRMS [M + H] = 442,3.

Ejemplo 124.

(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(pirrolidin–1–il)metanona.

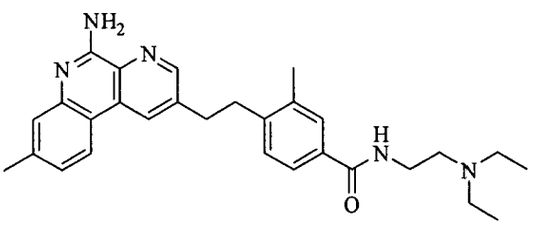


Se preparó (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(pirrolidin–1–il)metanona a partir de cloruro de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoílo (Ejemplo 116/Etapa 2) y pirrolidina, siguiendo los procedimientos descriptos para el Ejemplo 117. ^{1}H RMN (metanol– d_4): δ 8,60 (s, 1H), 8,42 (s, 1H), 8,09 (d, 1H), 7,34 (s, 1H), 7,23 (s, 1H),

7,05–7,15 (m, 3H), 3,49 (t, 2H), 3,27 (t, 2H), 3,05–3,17 (m, 4H), 2,42 (s, 3H), 2,26 (s, 3H), 1,88–1,91 (m, 2H), 1,73–1,77 (m, 2H). LRMS [M + H] = 425,2.

Ejemplo 125.

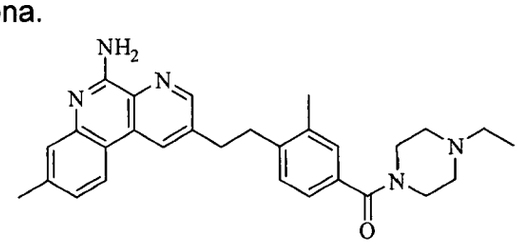
4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dietilamino)etil)–3–metilbenzamida.



Se preparó 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dietilamino)etil)–3–metilbenzamida a partir de cloruro de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoílo (Ejemplo 116/Etapa 2) y N^1,N^1–dietiletano–1,2–diamina, siguiendo los procedimientos descriptos para el Ejemplo 117. ^{1}H RMN (metanol– d_4): δ 8,55 (s, 1H), 8,48 (s, 1H), 8,10 (d, 1H), 7,56 (s, 1H), 7,47–7,50 (m, 1H), 7,33 (s, 1H), 7,10–7,14 (m, 2H), 3,44 (t, 2H), 3,25 (t, 2H), 3,08–3,14 (m, 4H), 2,62–2,72 (m, 4H), 2,42 (s, 3H), 2,27 (s, 3H), 1,05 (t, 6H). LRMS [M + H] = 470,3.

Ejemplo 126.

(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(4–etilpiperazin–1–il)metanona.

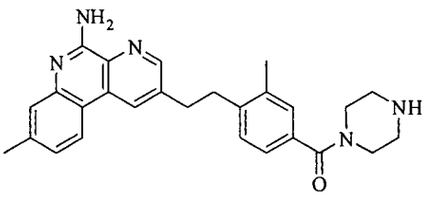


Se preparó (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(4–etilpiperazin–1–il)metanona a partir de cloruro de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoílo (Ejemplo 116/Etapa 2) y 1–etilpiperazina, siguiendo los procedimientos descriptos para el Ejemplo 117. ^{1}H RMN (Metanol– d_4): δ 8,59 (s, 1H), 8,37 (s, 1H), 8,06 (d, 1H), 7,32 (s, 1H), 7,00–

7,12 (m, 4H), 3,67 (br, 2H), 3,06–3,13 (m, 4H), 2,45 (br, 4H), 2,37 (q, 2H), 2,41 (s, 3H), 2,26 (s, 3H), 2,19 (br, 2H), 1,04 (t, 3H). LRMS [M + H] = 468,3.

Ejemplo 127.

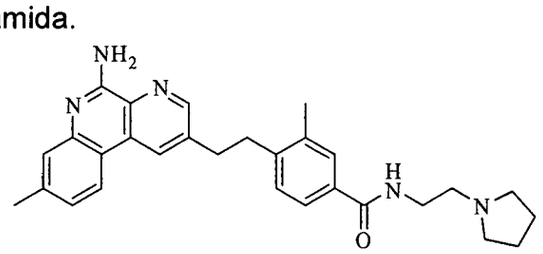
(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(piperazin–1–il)metanona.



Se preparó (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(piperazin–1–il)metanona a partir de cloruro de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoílo (Ejemplo 116/Etapa 2) y piperazina, siguiendo los procedimientos descriptos para el Ejemplo 117. ^{1}H RMN (metanol– d_4): δ 8,66 (s, 1H), 8,55 (s, 1H), 8,19 (d, 1H), 7,38 (s, 1H), 7,21–7,23 (m, 2H), 7,10–7,15 (m, 2H), 3,66 (br, 6H), 3,08–3,18 (m, 6H), 2,45 (s, 3H), 2,30 (s, 3H). LRMS [M + H] = 440,2.

Ejemplo 128.

4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metil–N–(2–(pirrolidin–1–il)etil)benzamida.

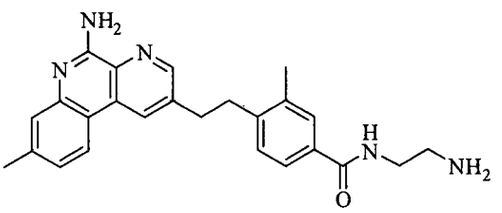


Se preparó 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metil–N–(2–(pirrolidin–1–il)etil)benzamida a partir de cloruro de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoílo (Ejemplo 116/Etapa 2) y 2–(pirrolidin–1–il)etanamina, siguiendo los procedimientos descriptos para el Ejemplo 117. ^{1}H RMN ($CDCl_3$): δ 8,58 (s, 1H), 8,38 (s, 1H), 8,07 (d, 1H), 7,64 (s, 1H), 7,51–7,55 (m, 2H), 7,12–7,20 (m, 2H), 6,26 (br, 2H), 3,61 (dd, 2H), 3,05–3,12

(m, 4H), 2,81 (t, 2H), 2,69 (br, 4H), 2,50 (s, 3H), 2,33 (s, 3H), 1,83–1,85 (m, 4H). LRMS [M + H] = 468,3.

Ejemplo 129.

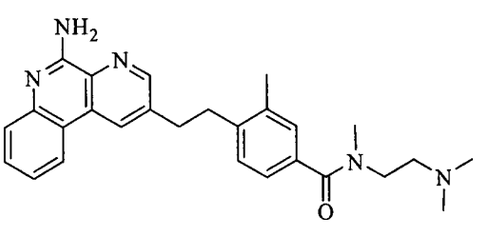
4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–aminoetil)–3–metilbenzamida.



Se preparó 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–aminoetil)–3–metilbenzamida a partir de cloruro de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoílo (Ejemplo 116/Etapa 2) y etano–1,2–diamina, siguiendo los procedimientos descriptos para el Ejemplo 117. ^{1}H RMN ($CDCl_3$): δ 8,59 (s, 1H), 8,37 (s, 1H), 8,07 (d, 1H), 7,63 (s, 1H), 7,51 (br, 2H), 7,12–7,21 (m, 2H), 6,25 (br, 2H), 3,48–3,52 (m, 2H), 3,08–3,15 (m, 4H), 2,94 (t, 2H), 2,51 (s, 3H), 2,34 (s, 3H). LRMS [M + H] = 414,2.

Ejemplo 130.

4–(2–(5–Aminobenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N,3–dimetilbenzamida.

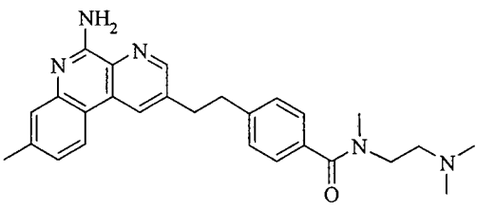


Se preparó 4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N,3–dimetilbenzamida a partir de cloruro de 4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoílo (Ejemplo 116/Etapa 2) y N^1,N^1,N^2–trimetiletano–1,2–diamina, siguiendo los procedimientos descriptos para el Ejemplo 117. ^{1}H RMN (metanol– d_4): δ 8,84 (s, 1H), 8,63 (s, 1H), 8,39 (d, 1H), 7,76–7,83 (m, 2H), 7,60–7,64 (m, 1H), 7,37 (s, 1H), 7,19–7,29 (m, 2H), 3,96 (t,

2H), 3,48 (t, 2H), 3,32 (t, 2H), 3,20 (t, 2H),3,09 (s, 3H), 3,06 (s, 6H), 2,42 (s, 3H). LRMS [M + H] = 442,3.

Ejemplo 131.

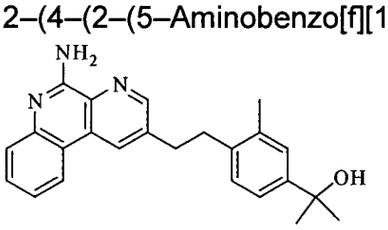
4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N–metilbenzamida.



Se preparó 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N–metilbenzamida a partir de cloruro de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoílo (Ejemplo 116/Etapa 2) y N^1,N^1,N^2–trimetiletano–1,2–diamina, siguiendo los procedimientos descriptos para el Ejemplo 117. ^{1}H RMN ($CDCl_3$): δ 8,64 (s, 1H), 8,36 (s, 1H), 8,05 (d, 1H), 7,60 (s, 1H), 7,41 (d, 2H), 7,31 (d, 1H), 7,21 (d, 2H), 3,91 (t, 2H), 3,44 (t, 2H), 3,25 (t, 2H), 3,12 (t, 2H),3,03 (s, 3H), 3,01 (s, 6H), 2,53 (s, 3H). LRMS [M + H] = 442,3.

Ejemplo 132.

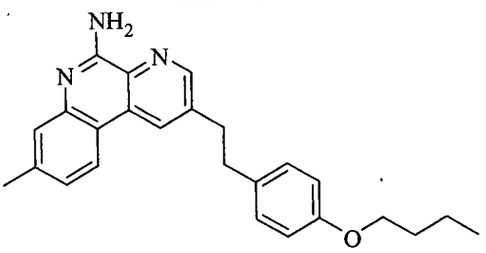
2–(4–(2–(5–Aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol.



Se preparó 2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol siguiendo los procedimientos descriptos para el Ejemplo 78, pero usando metil 4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato, que se preparó en forma análoga al Ejemplo 115 pero usando ter–butil 2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato en Etapa 4. LRMS [M + H] = 372,2.

Ejemplo 133.

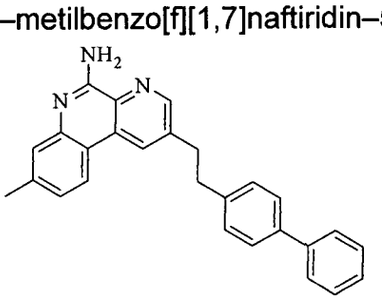
2–(4–Butoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.



Se preparó 2–(4–butoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina siguiendo los procedimientos descriptos para el Ejemplo 45/Etapas 1 a 3, pero usando 1–butoxi–4–etinilbenceno (comercial) con 3,5–dicloropicolinonitrilo (comercial) en la etapa 1. ^{1}H RMN (Acetona– d_6): δ 8,75 (s, 1H), 8,68 (s, 1H), 8,28 (d, 1H), 7,42 (s, 1H), 7,10–7,18 (m, 3H), 6,84 (d, 2H), 6,58 (br, 2H), 3,94 (t, 2H), 3,21 (t, 2H), 3,05 (t, 2H), 2,46 (s, 3H), 1,65–1,75 (m, 2H), 1,41–1,58 (m, 2H), 0,94 (s, 3H). LRMS [M + H] = 386,2.

Ejemplo 134.

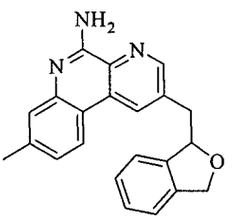
2–(2–(Bifenil–4–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina.



Se preparó 2–(2–(bifenil–4–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina siguiendo los procedimientos descriptos para el Ejemplo 45/Etapas 1 a 3, pero usando 4–etinilbifenilo (comercial) con 3,5–dicloropicolinonitrilo (comercial) en la etapa 1. ^{1}H RMN (Acetona– d_6): δ 8,80 (s, 1H), 8,75 (s, 1H), 8,26 (d, 2H), 7,55–7,69 (m, 4H), 7,30–7,46 (m, 4H), 7,13 (d, 2H), 6,58 (br, 2H), 3,30 (t, 2H), 3,18 (t, 2H), 2,45 (s, 3H). LRMS [M + H] = 390,2.

Ejemplo 135.

2–((1,3–Dihidroisobenzofuran–1–il)metil)–8–metilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 2–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)fenil)metanol.

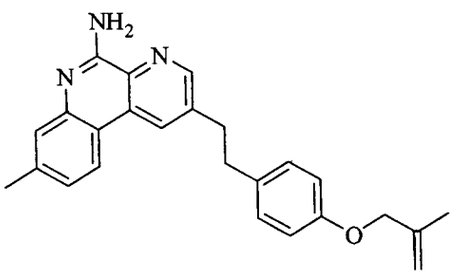
Se preparó 2–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)fenil)metanol siguiendo los procedimientos descriptos para el Ejemplo 45/Etapas 1 a 2, pero usando (2–etinilfenil)metanol (comercial) con 3,5–dicloropicolinonitrilo (comercial) en la Etapa 1.

Etapa 2: 2–((1,3–dihidroisobenzofuran–1–il)metil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

A una solución de 2–((5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etinil)fenil)metanol (1,0 equiv.) (de la etapa previa) en etanol (0,05 M) se agregó 10% en peso de paladio sobre carbón (0,2 equiv. en peso). Luego se introdujo gas hidrógeno por medio de un balón, y la reacción se dejó en agitación durante 18 horas. En este punto, la mezcla se filtró a través de una almohadilla de celite, lavando con metanol. Los volátiles se eliminaron al vacío, y el residuo resultante se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–60% de acetato de etilo en hexanos a fin de lograr 2–((1,3–dihidroisobenzofuran–1–il)metil)–8–metilbenzo[f][1,7]naftiridin–5–amina en forma de un sólido. ^{1}H RMN (Acetona– d_6): δ 8,78 (s, 1H), 8,74 (s, 1H), 8,24 (d, 2H), 7,40–7,44 (m, 2H), 7,20–7,34 (m, 3H), 6,61 (br, 2H), 5,63–5,69 (m, 1H), 4,89–5,00 (dd, 2H), 3,51–3,56 (dd, 1H), 3,28–3,34 (dd, 1H), 2,46 (s, 3H). LRMS [M + H] = 342,1.

Ejemplo 136.

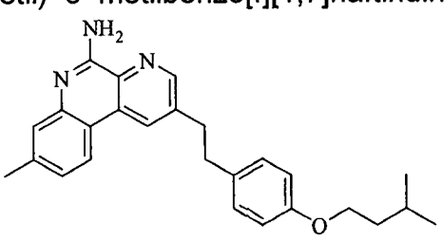
8–Metil–2–(4–(2–metilaliloxi)fenetil)benzo[f][1,7]naftiridin–5–amina.



A una solución de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol (del Ejemplo 170) (1,0 equiv.) en dimetilformamida (0,10 M) se agregó carbonato de potasio anhidro (1,5 equiv.), seguido de bromuro de metalilo (1,2 equiv.). La mezcla resultante se dejó agitar durante 18 horas a 100°C. Después de enfriar hasta temperatura ambiente, la mezcla se diluyó con acetato de etilo y agua. Las capas bifásicas se separaron, y la capa acuosa se lavó dos veces con acetato de etilo. Las capas orgánicas combinadas se secaron sobre Na_2SO_4 anhidro, y se eliminaron los volátiles al vacío. El residuo resultante se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–60% de acetato de etilo en hexanos, de manera de proporcionar 8–metil–2–(4–(2–metilaliloxi)fenetil)benzo[f][1,7]naftiridin–5–amina en forma de un sólido. ^{1}H RMN (Acetona– d_6): δ 8,75 (s, 1H), 8,68 (s, 1H), 8,27 (d, 1H), 7,41 (s, 1H), 7,12–7,19 (m, 3H), 6,87 (d, 2H), 6,60 (br, 2H), 5,06 (s, 1H), 4,93 (s, 1H), 4,43 (s, 2H), 3,20 (t, 2H), 3,05 (t, 2H), 2,45 (s, 3H), 1,79 (s, 3H). LRMS [M + H] = 384,2.

Ejemplo 137.

2–(4–(Isopentiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

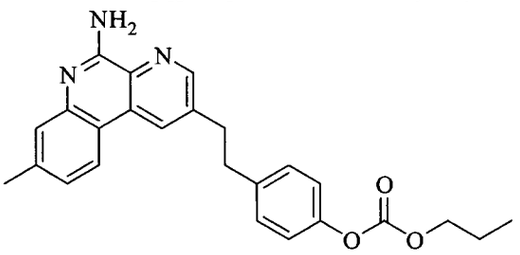


Se preparó 2–(4–(isopentiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina a partir de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol (del Ejemplo 170), siguiendo el procedimiento descripto para el Ejemplo 136, pero

usando 1–bromo–3–metilbutano. ^{1}H RMN (Acetona– d_6): δ 8,72 (s, 1H), 8,69 (s, 1H), 8,26 (d, 1H), 7,43 (s, 1H), 7,12–7,18 (m, 3H), 6,84 (d, 2H), 6,50 (br, 2H), 3,98 (t, 2H), 3,21 (t, 2H), 3,06 (t, 2H), 2,46 (s, 3H), 1,78–1,87 (m, 1H), 1,61–1,67 (dd, 2H), 0,96 (s, 3H), 0,95 (3H). LRMS [M + H] = 400,2.

Ejemplo 138.

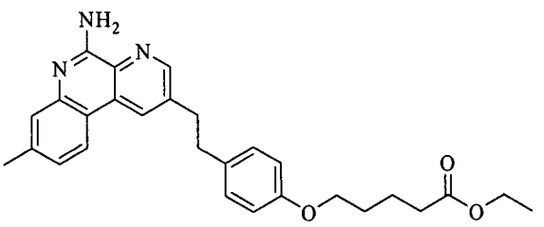
4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil propil carbonato.



A una solución de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol (del Ejemplo 170) (1,0 equiv.) y trietil amina (2 equiv.) en diclorometano (0,10 M) a 0°C se agregó cloroformiato de etilo (1,2 equiv.). La mezcla resultante se dejó agitar durante 30 minutos a 0°C, y luego se diluyó con agua y diclorometano. Las capas bifásicas se separaron, y la capa acuosa se lavó dos veces con diclorometano. Las capas orgánicas combinadas se secaron sobre Na_2SO_4 anhidro, y se eliminaron los volátiles al vacío. El residuo resultante se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–50% de acetato de etilo en hexanos, a fin de proporcionar 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil etil carbonato en forma de un sólido. ^{1}H RMN (Acetona– d_6): δ 8,78 (s, 1H), 8,73 (s, 1H), 8,28 (d, 1H), 7,43 (s, 1H), 7,33 (d, 2H), 7,10–7,17 (m, 3H), 6,64 (br, 2H), 4,18 (t, 2H), 3,25 (t, 2H), 3,14 (t, 2H), 2,45 (s, 3H), 1,68–1,77 (m, 2H), 0,97 (t, 3H). LRMS [M + H] = 416,2.

Ejemplo 139.

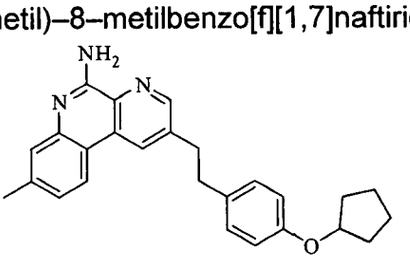
Etil 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)pentanoato.



A una solución de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol (del Ejemplo 170) (1,0 equiv.) en dimetilformamida (0,10 M) a 22°C se agregó una dispersión al 60% de hidruro de sodio en aceite mineral (1,5 equiv.), y la mezcla resultante se dejó agitar un período de 30 min. En este punto, se agregó a esta mezcla etil 5–bromopentanoato (1,2 equiv.). La mezcla de reacción luego se dejó agitar durante 18 horas, y a continuación, se diluyó con acetato de etilo y agua. Las capas bifásicas se separaron, y la capa orgánica se lavó dos veces con agua. La capa orgánica se secó sobre Na_2SO_4 anhidro, y los volátiles se eliminaron al vacío. El residuo resultante se purificó por medio de la RP–HPLC usando un gradiente de 10–50% de MeCN en agua. La sal de trifluoracetato resultante entonces se convirtió en la forma de base libre, utilizando una resina de intercambio iónico StratoSpheres™ PL–SO3H SPE, para obtener etil 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)pentanoato en forma de un sólido. ^{1}H RMN (Acetona– d_6): δ 8,80 (s, 1H), 8,74 (s, 1H), 8,33 (d, 1H), 7,47 (s, 1H), 7,24 (d, 1H), 7,17 (d, 2H), 6,85 (d, 2H), 4,10 (q, 2H), 3,97 (t, 2H), 3,25 (t, 2H), 3,07 (t, 2), 2,50 (s, 3H), 2,37 (t, 3H), 1,74–1,84 (m, 4H), 1,21 (t, 3H). LRMS [M + H] = 458,2.

Ejemplo 140.

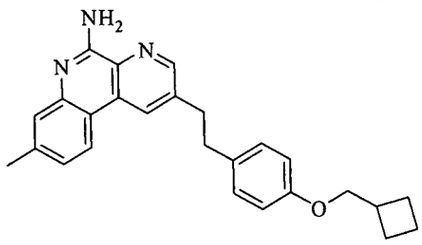
2–(4–(Ciclopentiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.



Se preparó 2–(4–(ciclopentiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina a partir de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol (del Ejemplo 170), siguiendo el procedimiento descripto para el Ejemplo 136, pero usando bromociclopentano. ^{1}H RMN (Acetona– d_6): δ 8,75 (d, 2H), 8,30 (d, 1H), 7,45 (s, 1H), 7,20 (d, 1H), 7,14 (d, 2H), 6,79 (d, 2H), 4,73–4,81 (m, 1H), 3,22 (t, 2H), 3,05 (t, 2H), 2,47 (s, 3H), 1,85–1,96 (m, 2H), 1,70–1,79 (m, 4H), 1,56–1,64 (m, 2H). LRMS [M + H] = 398,2.

Ejemplo 141.

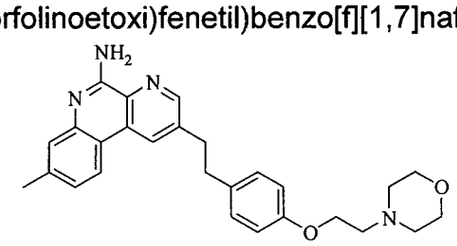
2–(4–(Ciclobutilmetoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.



Se preparó 2–(4–(ciclobutilmetoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina a partir de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol (del Ejemplo 170), siguiendo el procedimiento descripto para el Ejemplo 136, pero usando (bromometil)ciclobutano. ^{1}H RMN (Acetona– d_6): δ 8,79 (s, 1H), 8,73 (s, 1H), 8,33 (d, 1H), 7,47 (s, 1H), 7,26 (d, 1H), 7,16 (d, 2H), 6,82 (d, 2H), 3,90 (d, 2H), 3,23 (t, 2H), 3,06 (t, 2H), 2,68–2,79 (m, 1H), 2,49 (s, 3H), 2,05–2,14 (m, 2H), 1,80–1,98 (m, 4H). LRMS [M + H] = 398,2.

Ejemplo 142.

8–Metil–2–(4–(2–morfolinoetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina.

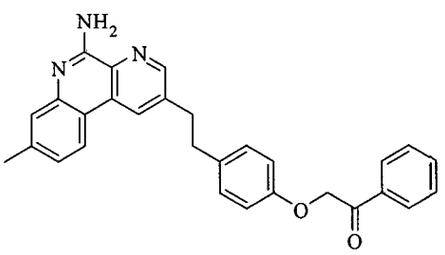


Se preparó 8–metil–2–(4–(2–morfolinoetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina a partir de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol (del

Ejemplo 170), siguiendo el procedimiento descripto para el Ejemplo 139, pero usando 4–(2–bromoetil)morfolina. ^{1}H RMN (Acetona– d_6): δ 8,78 (s, 1H), 8,72 (s, 1H), 8,30 (d, 1H), 7,46 (s, 1H), 7,17–7,24 (m, 3H), 6,85 (d, 2H), 4,08 (t, 2H), 3,56–3,62 (m, 4H), 3,45–3,53 (m, 2H), 3,24 (t, 2H), 3,07 (t, 2H), 2,73 (t, 2H), 2,52–2,56 (m, 2H), 2,49 (s, 3H). LRMS [M + H] = 443,2.

Ejemplo 143.

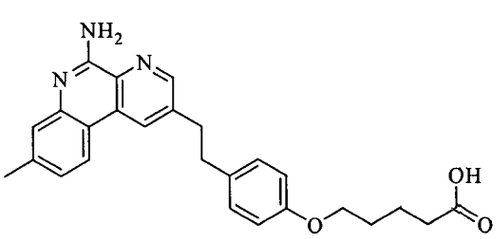
2–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)–1–feniletanona.



Se preparó 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)–1–feniletanona a partir de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol (del Ejemplo 170), siguiendo el procedimiento descripto para el Ejemplo 139, pero usando 2–bromo–1–feniletanona. ^{1}H RMN (Acetona– d_6): δ 8,76 (s, 1H), 8,71 (s, 1H), 8,27 (d, 1H), 8,06 (d, 2H), 7,67 (t, 1H), 7,57 (t, 2H), 7,43 (s, 1H), 7,17 (d, 3H), 6,90 (d, 2H), 5,45 (s, 2H), 3,21 (t, 2H), 3,06 (t, 2H), 2,45 (s, 3H). LRMS [M + H] = 448,2.

Ejemplo 144.

Ácido 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)pentanoico.

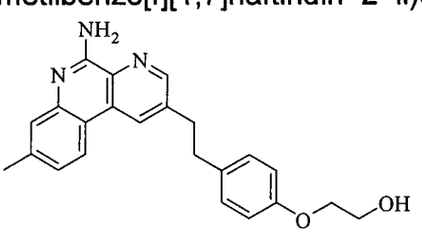


A una solución de etil 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)pentanoato (1,0 equiv.) (del Ejemplo 139) en etanol (0,10 M) se

agregó hidróxido de sodio anhidro (2,0 equiv.), y la mezcla resultante se dejó agitar a 80°C durante 2 horas. Después de enfriar hasta temperatura ambiente, la mezcla se diluyó con acetato de etilo y agua. Las capas bifásicas se separaron, y la capa acuosa se lavó dos veces con acetato de etilo. Las capas orgánicas combinadas se secaron sobre Na_2SO_4 anhidro, y se eliminaron los volátiles al vacío. El residuo resultante se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–10% de metanol en diclorometano, a fin de proporcionar ácido 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)pentanoico en forma de un sólido. ^{1}H RMN (Metanol– d_4): δ 8,61 (s, 1H), 8,57 (s, 1H), 8,20 (d, 1H), 7,40 (s, 1H), 7,20 (d, 1H), 7,07 (d, 2H), 6,81 (d, 2H), 3,93 (t, 2H), 3,18 (t, 2H), 3,00 (t, 2H), 2,48 (s, 3H), 2,25 (t, 2H), 1,74–1,81 (m, 2H), 0,86–0,96 (m, 2H). LRMS [M + H] = 430,2.

Ejemplo 145.

2–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)etanol.



Etapa 1: 2–(4–(2–(ter–butildimetilsililoxi)etoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

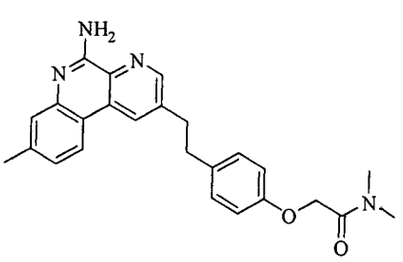
Se preparó 2–(4–(2–(ter–butildimetilsililoxi)etoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina a partir de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol (del Ejemplo 170), siguiendo el procedimiento descripto para el Ejemplo 139, pero usando (2–bromoetoxi)(ter–butil)dimetilsilano.

Etapa 2: 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)etanol.

A una solución de 2–(4–(2–(ter–butildimetilsililoxi)etoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina (de la etapa previa) (1,0 equiv.) en tetrahidrofurano (0,10 M) se agregó una solución, 1,0 M, de fluoruro de tetrabutilamonio (5 equiv.) en THF, y la mezcla resultante se dejó agitar a 22°C durante 2 horas. En este punto, la mezcla se diluyó con acetato de etilo y agua. Se separaron las capas bifásicas, y la capa acuosa se lavó dos veces con acetato de etilo. Las capas orgánicas combinadas se secaron sobre Na_2SO_4 anhidro, y se eliminaron los volátiles al vacío. El residuo resultante se purificó por medio de un sistema COMBIFLASH® (ISCO) usando 0–10% de metanol en diclorometano, de manera de obtener 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)etanol en forma de un sólido. ^{1}H RMN (Acetona– d_6): δ 8,76 (s, 1H), 8,67 (s, 1H), 8,28 (d, 1H), 7,40 (s, 1H), 7,15 (t, 3H), 6,84 (d, 2H), 6,54 (br, 2H), 4,00 (t, 2H), 3,83 (t, 2H), 3,21 (t, 2H), 3,05 (t, 2H), 2,45 (s, 3H). LRMS [M + H] = 374,2.

Ejemplo 146.

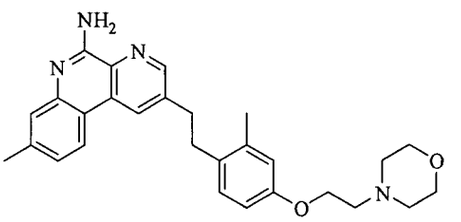
2–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)–N,N–dimetilacetamida.



Se preparó 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)–N,N–dimetilacetamida a partir de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol (del Ejemplo 170) y siguiendo el procedimiento descripto para el Ejemplo 139, pero usando 2–bromo–*N*,*N*–dimetilacetamida. ^{1}H RMN (Acetona– d_6): δ 8,75 (s, 1H), 8,70 (s, 1H), 8,28 (d, 1H), 7,40 (s, 1H), 7,18 (t, 3H), 6,87 (d, 2H), 6,56 (br, 2H), 4,72 (s, 2H), 3,20 (t, 2H), 3,07 (s, 3H), 3,05 (t, 2H), 2,87 (s, 3H), 2,45 (s, 3H). LRMS [M + H] = 415,2.

Ejemplo 147.

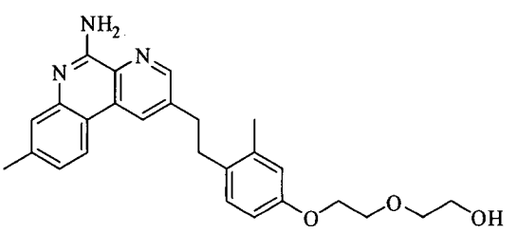
8–Metil–2–(2–metil–4–(2–morfolinoetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina.



Se preparó 8–metil–2–(2–metil–4–(2–morfolinoetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina siguiendo un procedimiento análogo a la preparación descripta para el Ejemplo 139, pero usando 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol (del Ejemplo 50) y 4–(2–bromoetil)morfolina. ^{1}H RMN (Acetona– d_6): δ 8,73 (d, 2H), 8,26 (d, 1H), 7,44 (s, 1H), 7,17 (d, 1H), 7,05 (d, 1H), 6,76 (s, 1H), 6,67 (d, 1), 4,04–4,08 (m, 3H), 3,60–3,62 (m, 4H), 3,30 (s, 1H), 3,16 (t, 2H), 3,04 (t, 2H), 2,71 (t, 2H), 2,50–2,52 (m, 2H), 2,47 (s, 3H), 2,28 (s, 3H). LRMS [M + H] = 457,3.

Ejemplo 148.

2–(2–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etanol.



Etapa 1: 2–(4–(2–(2–(ter–butildimetilsililoxi)etoxi)etoxi)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

Se preparó 2–(4–(2–(2–(ter–butildimetilsililoxi)etoxi)etoxi)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina siguiendo un procedimiento análogo a la preparación descripta para el Ejemplo 145/Etapa 1, pero usando 4–(2–(5–amino–

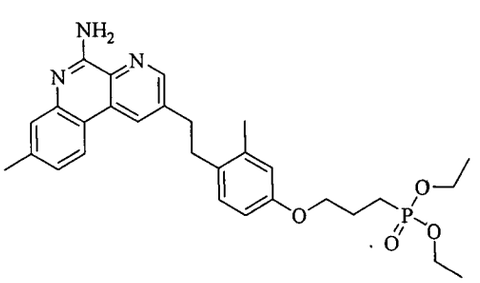
8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol (del Ejemplo 50) con ter–butil(2–(2–cloroetoxi)etoxi)dimetilsilano.

Etapa 2: 2–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etanol.

Se preparó 2–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etanol a partir de 2–(4–(2–(2–(ter–butildimetilsililoxi)etoxi)etoxi)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 145/Etapa 2. ^{1}H RMN (Acetona– d_6): δ 8,74 (s, 1H), 8,69 (s, 1H), 8,27 (d, 1H), 7,41 (s, 1H), 7,14 (d, 1H), 7,06 (d, 1H), 6,75 (s, 1H), 6,69 (d, 1), 6,54 (br, 2H), 4,07 (t, 2H), 3,79 (t, 2H), 3,64 (t, 2H), 3,59 (t, 2H), 3,16 (t, 2H), 3,03 (t, 2H), 2,45 (s, 3H), 2,29 (s, 3H). LRMS [M + H] = 432,2.

Ejemplo 149.

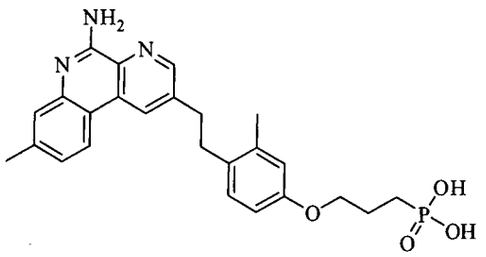
Dietil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propilfosfonato.



Se preparó dietil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propilfosfonato siguiendo un procedimiento análogo a la preparación descripta para el Ejemplo 139, pero usando 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol (del Ejemplo 50) con dietil 3–bromopropilfosfonato. ^{1}H RMN (Acetona– d_6): δ 9,52 (s, 1H), 9,47 (s, 1H), 9,03 (d, 1H), 8,21 (s, 1H), 7,93 (d, 1H), 7,84 (d, 1H), 7,60 (br, 2H), 7,53 (s, 1), 7,45 (d, 1H), 4,76–4,91 (m, 6H), 3,93 (t, 2H), 3,81 (t, 2H), 3,24 (s, 3H), 3,06 (s, 3H), 2,76–2,86 (m, 2H), 2,61–2,72 (m, 2H), 2,07 (t, 6H). LRMS [M + H] = 522,2.

Ejemplo 150.

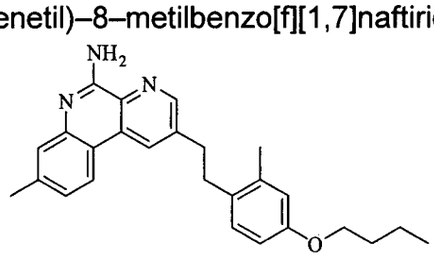
Ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propilfosfónico.



Una solución de ácido clorhídrico, 12 N (0,10 M) se agregó a dietil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propilfosfonato (del Ejemplo 149), y la mezcla resultante se dejó agitar a 100°C durante 18 horas. En este punto, se eliminó el ácido clorhídrico a presión reducida, y el residuo resultante se purificó por medio de la RP–HPLC usando un gradiente de 10–50% de MeCN en agua. La sal de trifluoracetato resultante luego se convirtió en la forma de base libre mediante la adición de una solución acuosa saturada de bicarbonato de sodio, seguida del lavado, tres veces, con acetato de etilo. Las capas orgánicas combinadas se secaron con Na_2SO_4 anhidro, y se eliminaron los volátiles al vacío a fin de suministrar ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propilfosfónico en forma de un sólido. ^{1}H RMN (Dimetilsulfóxido– d_6): δ 9,72 (br, 1H), 9,01 (s, 1H), 8,96 (br, 1H), 8,85 (s, 1H), 8,54 (d, 1H), 7,54 (s, 1H), 7,42 (d, 1H), 7,08 (d, 1), 6,74 (s, 1H), 6,66 (d, 1H), 3,95 (t, 2H), 3,14 (t, 2H), 2,97 (t, 2H), 2,50 (s, 3H), 2,27 (s, 3H), 1,81–1,91 (m, 2H), 1,56–1,67 (m, 2H). LRMS [M + H] = 466,2.

Ejemplo 151.

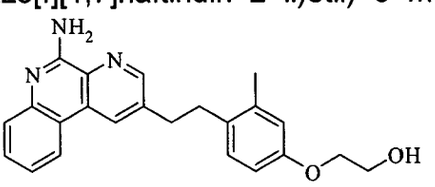
2–(4–Butoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.



Se preparó 2–(4–butoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina siguiendo un procedimiento análogo a la preparación descripta para el Ejemplo 139, pero usando 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol (del Ejemplo 50) con 1–bromobutano. ^{1}H RMN (Acetona– d_6): δ 8,75 (s, 1H), 8,71 (s, 1H), 8,28 (d, 1H), 7,43 (s, 1H), 7,15 (d, 1H), 7,07 (d, 1H), 6,75 (s, 1H), 6,69 (d, 1H), 6,54 (br, 2H) 3,95 (t, 2H), 3,16 (t, 2H), 3,04 (t, 2H), 2,47 (s, 3H), 2,30 (s, 3H), 1,69–1,77 (m, 2H), 1,43–1,54 (m, 2H), 0,97 (t, 3H). LRMS [M + H] = 400,2.

Ejemplo 152.

2–(4–(2–(5–Aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol.



Etapa 1: 4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol.

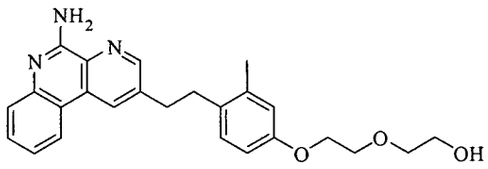
Se preparó 4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol siguiendo un procedimiento análogo a la preparación descripta para el Ejemplo 145, pero usando 2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–5–amina (del Ejemplo 119).

Etapa 2: 2–(4–(2–(5–Aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol.

Se preparó 2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol a partir de 4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 145/Etapas 1 a 2. LRMS [M + H] = 374,2.

Ejemplo 153.

2–(4–(2–(5–Aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol.



Etapa 1: 4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol

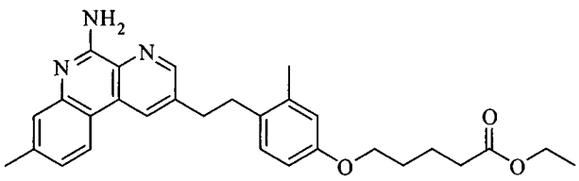
Se preparó 4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol siguiendo un procedimiento análogo a la preparación descripta para el Ejemplo 50, pero usando 2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–5–amina (del Ejemplo 119).

Etapa 2: 2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol.

Se preparó 2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol siguiendo los procedimientos descriptos para el Ejemplo 148/Etapas 1 a 2. LRMS [M + H] = 418,2.

Ejemplo 154.

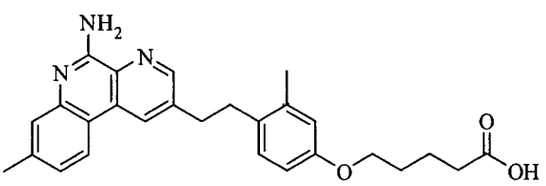
Etil 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)pentanoato.



Se preparó etil 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)pentanoato a partir de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol (del Ejemplo 50), siguiendo el procedimiento descripto para el Ejemplo 139, pero usando etil 5–bromopentanoato. ^{1}H RMN (CDCl3): δ 8,64 (s, 1H), 8,27 (s, 1H), 8,02 (d, 1H), 7,66 (s, 1H), 7,32 (d, 1H), 6,91 (d, 1H), 6,66 (s, 1H), 6,63 (d, 1H), 4,13 (q, 2H), 3,93 (t, 2H), 3,14 (t, 2H), 2,99 (t, 2H), 2,54 (s, 3H), 2,38 (t, 2H), 2,25 (s, 3H), 1,79–1,83 (m, 4H), 1,26 (t, 3H). LRMS [M + H] = 472,3.

Ejemplo 155.

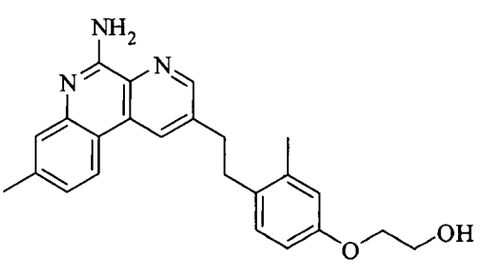
Ácido 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)pentanoico.



Se preparó ácido 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)pentanoico a partir de etil 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)pentanoato (de la etapa previa), siguiendo el procedimiento descripto para el Ejemplo 144. ^{1}H RMN (CDCl3): δ 8,52 (s, 1H), 8,27 (s, 1H), 8,02 (d, 1H), 7,65 (s, 1H), 7,32 (d, 1H), 6,86 (d, 1H), 6,72 (s, 1H), 6,63 (d, 1H), 3,95 (t, 2H), 3,15 (t, 2H), 2,99 (t, 2H), 2,54 (s, 3H), 2,45 (t, 2H), 2,23 (s, 3H), 1,79–1,83 (m, 4H). LRMS [M + H] = 444,2.

Ejemplo 156.

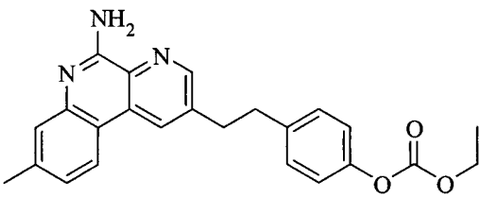
2–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol.



Se preparó 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol siguiendo los procedimientos descriptos para el Ejemplo 145/Etapas 1 a 2, pero usando 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol (del Ejemplo 50). ^{1}H RMN (Acetona– d_6): δ 8,76 (s, 1H), 8,69 (s, 1H), 8,28 (d, 1H), 7,40 (s, 1H), 7,15 (d, 1H), 7,09 (d, 1H), 6,75 (s, 1H), 6,68 (d, 1H), 6,57 (br, 2H), 4,00 (t, 2H), 3,79–3,88 (m, 2H), 3,17 (t, 2H), 3,04 (t, 2H), 2,46 (s, 2H), 2,29 (s, 2H). LRMS [M + H] = 388,5.

Ejemplo 157.

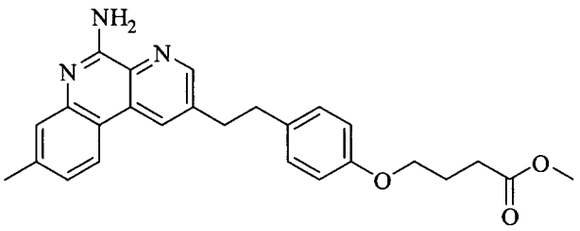
4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil etil carbonato.



Se preparó 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil etil carbonato a partir de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol (del Ejemplo 170), siguiendo el procedimiento descripto para el Ejemplo 138, pero usando etil carbonocloridato. LRMS [M + H] = 402,2.

Ejemplo 158.

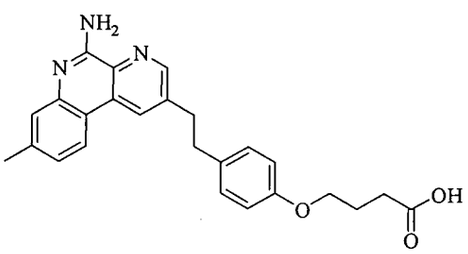
Metil 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)butanoato.



Se preparó metil 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)butanoato a partir de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol (del Ejemplo 170), siguiendo el procedimiento descripto para la preparación del Ejemplo 139, pero usando metil 4–bromobutanoato. ^{1}H RMN (Acetona– d_6): δ 8,74 (s, 1H), 8,67 (s, 1H), 8,24 (d, 1H), 7,39 (s, 1H), 7,09–7,19 (m, 3H), 6,82 (d, 2H), 6,53 (br, 2H), 3,97 (t, 2H), 3,60 (s, 3H), 3,19 (t, 2H), 3,04 (t, 2H), 2,48 (t, 2H), 2,44 (s, 3H), 0,84–0,91 (m, 2H). LRMS [M + H] = 430,2.

Ejemplo 159.

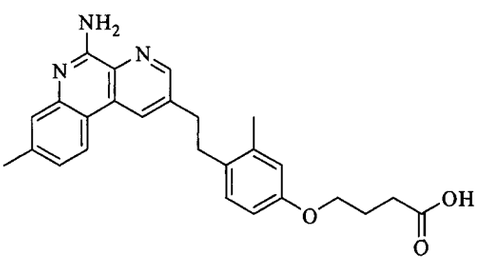
Ácido 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)butanoico.



Se preparó ácido 4–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)butanoico a partir de metil 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)butanoato (de la etapa previa), siguiendo el procedimiento descripto para el Ejemplo 144. ^{1}H RMN (Acetona– d_6): δ 7,47 (s, 1H), 7,41 (s, 1H), 7,09 (d, 1H), 6,21 (s, 1H), 6,18 (d, 1H), 5,82 (d, 2H), 5,52 (d, 2H), 2,66 (t, 2H), 1,99 (t, 2H), 1,77 (t, 2H), 1,28 (s, 3H), 1,17 (t, 2H), 0,70–0,79 (m, 2H). LRMS [M + H] = 416,2.

Ejemplo 160.

Ácido 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)butanoico.



Etapa 1: metil 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)butanoato.

Se preparó metil 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)butanoato siguiendo el mismo procedimiento que aquel descripto para el Ejemplo 158, pero usando 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol (del Ejemplo 50).

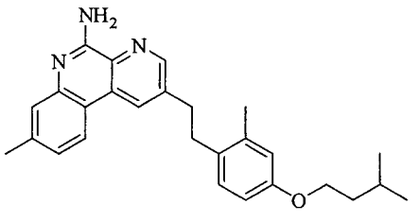
Etapa 2: ácido 4–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)butanoico.

Se preparó ácido 4–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)butanoico a partir de metil 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)butanoato (de la etapa previa), siguiendo el procedimiento descripto para el Ejemplo 144. ^{1}H RMN (Acetona– d_6): δ 8,38 (s, 1H), 8,24 (s, 1H), 7,90 (d, 1H), 6,90 (s, 1H), 6,68 (d, 1H), 6,54–6,63 (m,

2H), 6,27 (d, 1H), 6,20 (d, 1H), 3,40 (t, 2H), 2,62 (t, 2H), 2,47 (t, 2H), 1,99 (s, 3H), 1,80 (s, 2H), 1,45 (t, 2H), 1,27–1,39 (m, 2H). LRMS [M + H] = 430,2.

Ejemplo 161.

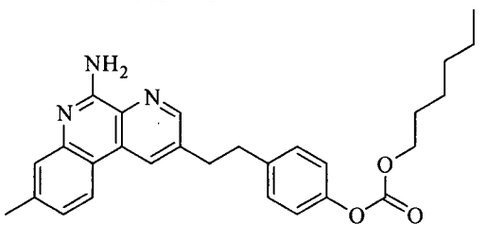
2–(4–(Isopentiloxi)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.



Se preparó 2–(4–(Isopentiloxi)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina a partir de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol (del Ejemplo 50), siguiendo el procedimiento descripto para el Ejemplo 136, pero usando 1–bromo–3–metilbutano. ^{1}H RMN (Acetona– d_6): δ 8,75 (s, 1H), 8,72 (s, 1H), 8,29 (d, 1H), 7,43 (s, 1H), 7,17 (D, 1H), 7,10 (d, 1H), 6,76 (d, 1H), 6,68(d, 1H), 6,56 (br, 2H), 4,00 (t, 2H), 3,17 (t, 2H), 3,07 (t, 2H), 2,48 (s, 3H), 1,76–1,91 (m, 1H), 1,60–1,71 (m, 2H), 0,96 (s, 6H). LRMS [M + H] = 414,2.

Ejemplo 162.

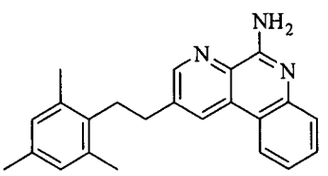
4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil hexil carbonato.



Se preparó 4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil hexil carbonato a partir de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol (del Ejemplo 170), siguiendo los procedimientos descriptos para el Ejemplo 138, pero usando hexil carbonocloridato. LRMS [M + H] = 458,2.

Ejemplo 163.

2–(2,4,6–Trimetilfenetil)benzo[f][1,7]naftiridin–5–amina.



Etapa 1: 2–(mesitiletinil)benzo[f][1,7]naftiridin–5–amina.

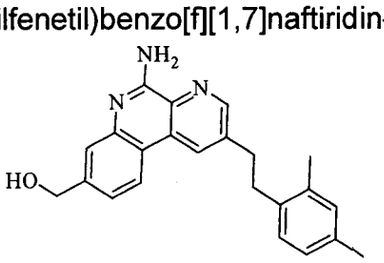
Se preparó 2–(mesitiletinil)benzo[f][1,7]naftiridin–5–amina a partir de 3–cloro–5–(mesitiletinil)picolinonitrilo (Ejemplo 77/Etapa 1) y *ter*–butil 2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (comercial), siguiendo los procedimientos descriptos para el Ejemplo 45/Etapa 1.

Etapa 2: 2–(2,4,6–Trimetilfenetil)benzo[f][1,7]naftiridin–5–amina.

Se preparó 2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina a partir de 2–(mesitiletinil)benzo[f][1,7]naftiridin–5–amina (de la etapa previa), siguiendo los procedimientos descriptos para el Ejemplo 45/Etapas 2 a 3. ^{1}H RMN (Acetona– d_6): δ 8,80 (s, 2H), 8,38 (d, 1H), 7,60 (d, 2H), 7,54 (d, 2H), 7,31 (t, 1H), 6,84 (s, 2H), 6,61 (br, 2H), 3,08 (s, 2H), 2,30 (s, 6H), 2,23 (s, 3H). LRMS [M + H] = 342,2.

Ejemplo 164.

(5–Amino–2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–8–il)metanol.



Etapa 1: metil 5–amino–2–((2,4–dimetilfenil)etinil)benzo[f][1,7]naftiridina–8–carboxilato.

Se preparó metil 5–amino–2–((2,4–dimetilfenil)etinil)benzo[f][1,7] naftiridina–8–carboxilato a partir de 3–cloro–5–((2,4–d metilfenil) etinil)picolinonitrilo (del Ejemplo 47/Etapa 3) y ácido 2–(*ter*–butoxicarbonilamino)–4–(metoxicarbonil) fenilbórico (del Ejemplo 85/Etapa1), siguiendo los procedimientos descriptos en el Ejemplo 95/etapa 1.

Etapa 2: metil 5–amino–2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridina–8–carboxilato.

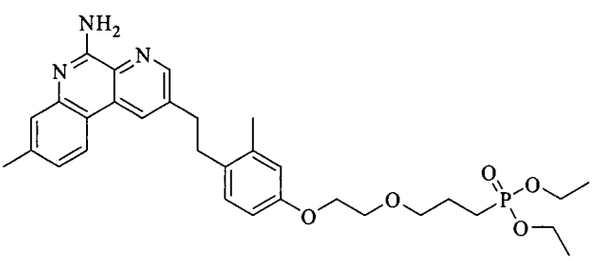
Se preparó metil 5–amino–2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridina–8–carboxilato a partir de metil 5–amino–2–((2,4–dimetilfenil)etinil) benzo[f][1,7]naftiridina–8–carboxilato (de la etapa previa), siguiendo los procedimientos descriptos en el Ejemplo 44/Etapa 5.

Etapa 3: (5–amino–2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–8–il)metanol.

Se preparó (5–amino–2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–8–il)metanol a partir de metil 5–amino–2–(2,4–dimetilfenetil)benzo[f][1,7] naftiridina–8–carboxilato (de la etapa previa), siguiendo los procedimientos descriptos en el Ejemplo 95/Etapa 2. ^{1}H RMN (Acetona– d_6): δ 8,79 (s, 1H), 8,73 (s, 1H), 8,35 (d, 1H), 7,61 (s, 1H), 7,34 (d, 1H), 7,08 (d, 1H), 6,97 (s, 1H), 6,91 (d, 1H), 6,51 (br, 2H), 4,77 (s, 2H), 3,16–3,20 (m, 2H), 3,04–3,10 (m, 2H), 2,28 (s, 3H), 2,25 (s, 3H). LRMS [M + H] = 358,2.

Ejemplo 165.

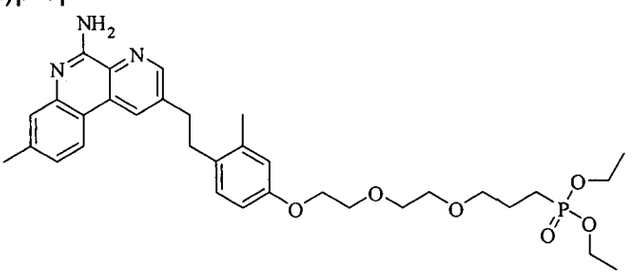
Dietil 3–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)propilfosfonato.



Se preparó dietil 3–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)propilfosfonato siguiendo el procedimiento descripto para el Ejemplo 139, pero usando 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol (del Ejemplo 156) y dietil 3–(2–bromoetoxi)propilfosfonato. LRMS [M + H] = 566,3.

Ejemplo 166.

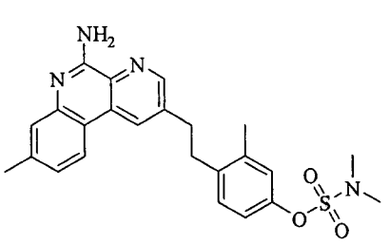
Dietil 3–(2–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etoxi)propilfosfonato.



Se preparó dietil 3–(2–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etoxi)propilfosfonato siguiendo el procedimiento descripto para el Ejemplo 139, pero usando 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol (del Ejemplo 148) y dietil 3–(2–(2–bromoetoxi)etoxi)propilfosfonato. ^{1}H RMN (Acetona– d_6): δ 8,75 (s, 1H), 8,70 (s, 1H), 8,26 (d, 1H), 7,42 (s, 1H), 7,16 (d, 1H), 7,09 (d, 1H), 6,77 (s, 1H), 6,71 (d, 1H), 6,58 (br, 2H), 3,95–4,11 (m, 6H), 3,76–3,80 (m, 2H), 3,63–3,67 (m, 2H), 3,55–3,58 (m, 2H), 3,57–3,51 (m, 2H), 3,14–3,18 (m, 2H), 3,04–3,05 (m, 2H), 2,46 (s, 3H), 2,29 (s, 3H), 1,71–1,87 (m, 4H), 1,22–1,29 (m, 8H). LRMS [M + H] = 610,3.

Ejemplo 167.

4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil dimetilsulfamato.

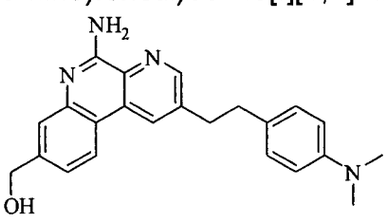


Se preparó 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil dimetilsulfamato a partir de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol (del Ejemplo 50), siguiendo el procedimiento descripto para el Ejemplo 138, pero usando cloruro de

dimetilsulfamoílo. ^{1}H RMN (Acetona– d_6): δ 8,79 (s, 1H), 8,72 (s, 1H), 8,28 (d, 1H), 7,42 (s, 1H), 7,27 (d, 1H), 7,17 (s, 1H), 7,14 (t, 1H), 7,05–7,10 (d, 1H), 3,19–3,25 (m, 2H), 3,11–3,17 (m, 2H), 2,92 (s, 6H), 2,46 (s, 3H), 2,37 (s, 3H). LRMS [M + H] = 451,2.

Ejemplo 168.

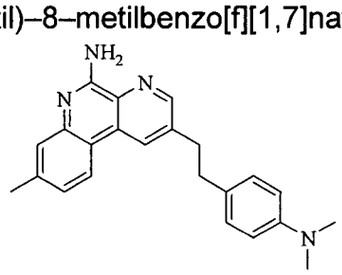
(5–Amino–2–(4–(dimetilamino)fenetil)benzo[f][1,7]naftiridin–8–il)metanol.



Se preparó (5–amino–2–(4–(dimetilamino)fenetil)benzo[f][1,7]naftiridin–8–il)metanol a partir de *ter*–butil 5–((*ter*–butildimetilsililoxi)metil)–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (del Ejemplo 99/etapa 1) y 4–etinil–N,N–dimetilanilina (comercial), siguiendo los procedimientos descriptos en el Ejemplo 45/Etapas 1 a 4, y luego, la desprotección del grupo TBS como en el Ejemplo 99/Etapa 3. ^{1}H RMN (Acetona– d_6): δ 8,78 (s, 1H), 8,73 (s, 1H), 8,35 (d, 1H), 7,61 (s, 1H), 7,31–7,35 (d, 1H), 7,08 (d, 1H), 6,68 (d, 2H), 6,50 (br, 2H), 4,78 (s, 2H), 4,34 (s, 1H), 3,16–3,20 (m, 2H), 3,03–3,10 (m, 2H), 2,83 (s, 3H), 2,80 (s, 3H). LRMS [M + H] = 373,2.

Ejemplo 169.

2–(4–(Dimetilamino)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

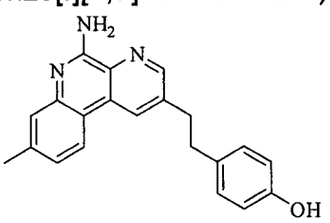


Se preparó 2–(4–(dimetilamino)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina siguiendo los procedimientos descriptos para el Ejemplo 45/Etapas 1 a 3, pero usando 4–etinil–*N,N*–dimetilanilina en la etapa 1. ^{1}H RMN (Acetona– d_6)

Base libre: δ 8,60 (s, 1H), 8,55 (s, 1H), 8,15 (d, 1H), 7,28 (s, 1H), 7,03 (d, 1H), 6,96 (d, 2H), 6,56 (d, 2H), 6,55 (br s, 2H), 3,05 (t, 2H), 2,88 (t, 2H), 2,75 (s, 6H), 2,33 (s, 3H). LRMS [M + H] = 357,2.

Ejemplo 170.

4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol.



Etapa 1: 2–(4–metoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

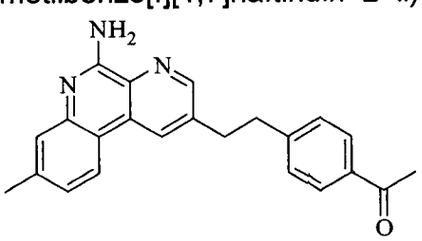
Se preparó 2–(4–metoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina siguiendo los procedimientos descriptos para el Ejemplo 79/Etapas 1 a 3, pero usando 1–etinil–4–metoxibenceno en la Etapa 1.

Etapa 2: 4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol.

Se preparó 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol a partir de 2–(4–metoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina (de la etapa previa), siguiendo el procedimiento descripto para el Ejemplo 50. ^{1}H RMN (Metanol– d_4): δ 8,59.

Ejemplo 171.

1–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona.



Etapa 1: 5–((4–acetilfenil)etinil)–3–cloropicolinonitrilo.

Una solución de 1–(4–etinilfenil)etanona (comercial) (1 eq.) 3,5–dicloropicolinonitrilo (1 eq.), diclorobis(trifenilfosfina)–paladio (II) (20% en moles), yoduro de cobre (10% en moles) y DMF:Trietilamina (10:1) (0,13 M) se agitó a

temperatura ambiente durante la noche. La mezcla de reacción luego se diluyó con acetato de etilo y solución de bicarbonato de sodio. Se separaron las dos fases, y la fase acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio, y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–100% de acetato de etilo en hexano, y se aisló 5–((4–acetilfenil)etinil)–3–cloropicolinonitrilo en forma de un sólido de color amarillo.

Etapa 2: 5–(4–acetilfenetil)–3–cloropicolinonitrilo.

A una solución de 5–((4–acetilfenil)etinil)–3–cloropicolinonitrilo (de la etapa previa) (1 eq.) en etanol (0,1 M) se agregó óxido de platino (30% en moles). Se introdujo gas hidrógeno por medio de un balón, y la reacción se agitó durante 0,5 horas. La mezcla se filtró a través de una almohadilla de celite, lavando con diclorometano. El filtrado se concentró al vacío y se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–100% de acetato de etilo en hexano, a fin de lograr 5–(4–acetilfenetil)–3–cloropicolinonitrilo en forma de un sólido blanquecino.

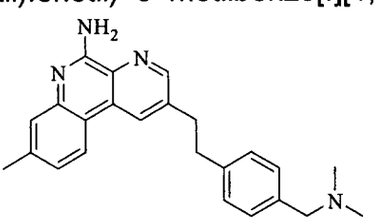
Etapa 3: 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona.

Una solución de *5–(4–acetilfenetil)–3–cloropicolinonitrilo* (de la etapa previa) (1 eq.) y ter–butil 5–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (1,0 eq.), tetraquis(trifenil–fosfina)paladio (10% en moles) y solución acuosa de carbonato de sodio, 2 N (2,0 eq.), en tolueno/etanol (1:1, 0,09 M) se calentó en condiciones de microondas usando un instrumento BIOTAGE INITIATOR 2.0 a 150^{0}C durante 20 minutos. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con etanol/agua. Los sólidos insolubles se separaron mediante la filtración, y el filtrado se concentró al

vacío de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona en forma de un sólido de color amarillo. ^{1}H RMN (Metanol– d_4) Sal de TFA: δ 8,69 (d, 2H), 8,30 (d, 1H), 7,80 (d, 2H), 7,3 8 (s, 1H), 7,36(d, 1H), 7,28 (d, 2H), 3,25 (t, 2H), 3,13 (t, 2H), 2,47 (s, 3H), 2,45 (s, 3H). LRMS [M + H] = 356,2.

Ejemplo 172.

2–(4–((Dimetilamino)metil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.



Etapa 1: 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzaldehído.

Se preparó 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzaldehído a partir de 4–etinilbenzaldehído (comercial), siguiendo los procedimientos descriptos para el Ejemplo 171/Etapas 1 a 3.

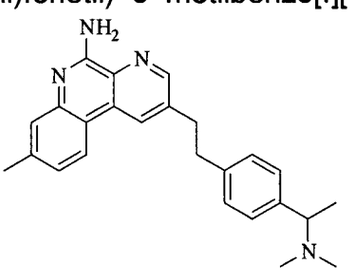
Etapa 2: 2–(4–((dimetilamino)metil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

Una solución de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzaldehído (de la etapa previa) (1 eq.), acetato de sodio (3,5 eq.) y N, N'–dimetil amina clorhidrato (3,5 eq.) disuelta en 1–2, dicloroetano (0,04 M) se calentó a 80^{0}C durante 2 horas en un vial sellado. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se enfrió adicionalmente hasta 0^{0}C, y se le agregó tri–acetoxi borohidruro de sodio (1,25 eq.). La mezcla de reacción se agitó a temperatura ambiente durante una hora. La mezcla se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la capa acuosa se extrajo

dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la HPLC preparatoria usando 10–90% de acetonitrilo/agua como el gradiente, y se aisló 2–(4–((dimetilamino)metil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina en forma de un polvo blanquecino como una sal de TFA. ^{1}H RMN (Metanol– d_4) Sal de TFA: δ 8,83 (s, 1H), 8,81 (s, 1H), 8,41 (d, 1H), 7,52 (s, 1H), 7,45 (d, 1H), 7,43 (s, 1H), 7,40 (m, 3H), 4,29 (s, 2H), 3,30–3,24 (m, 4H), 2,79 (s, 6H), 2,60 (s, 3H). LRMS [M + H] = 371,2.

Ejemplo 173.

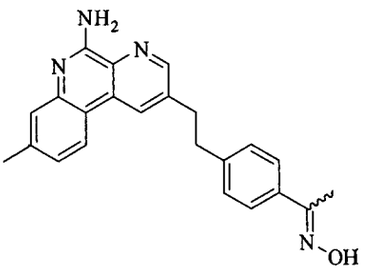
2–(4–(1–(Dimetilamino)etil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.



Se preparó 2–(4–(1–(dimetilamino)etil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina a partir de 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona (del Ejemplo 171), siguiendo los procedimientos descriptos para el Ejemplo 172/Etapa 2. ^{1}H RMN (Metanol– d_4) Sal de TFA: δ 8,84 (s, 1H), 8,79 (s, 1H), 8,40 (d, 1H), 7,52 (s, 1H), 7,44 –7,46 (m, 2H), 7,38–7,42 (m, 3H), 4,45 (m, 1H), 3,31 (t, 2H), 3,19 (t, 2H), 2,83 (s, 3H), 2,66 (s, 3H), 2,56 (s, 3H), 1,70 (d, 3H). LRMS [M + H] = 385,2.

Ejemplo 174.

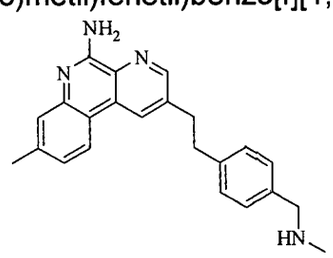
1–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona oxima.



Una solución de 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona (del Ejemplo 171) (1 eq.), clorhidrato de hidroxilamina (2 eq.) y 1 gota de HOAc, disuelta en etanol absoluto (0,028 M) se agitó a temperatura ambiente un lapso de 1,5 horas. La mezcla se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 10–80% de acetato de etilo en hexano, a fin de lograr 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona oxima como un sólido de color blanco. ^{1}H RMN (Metanol– d_4): δ 8,56 (s, 1H), 8,52 (s, 1H), 8,12 (d, 1H), 7,45 (d, 2H), 7,31 (s, 1H), 7,12 (m, 3H), 4,51 (s, OH), 3,15 (t, 2H), 3,01 (t, 2H), 2,39 (s, 3H), 2,09 (s, 3H). LRMS [M + H] = 371,2.

Ejemplo 175.

8–Metil–2–(4–((metilamino)metil)fenetil)benzo[f][1,7]naftiridin–5–amina.

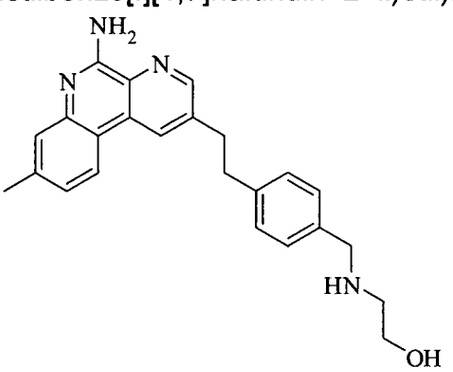


Se preparó 8–metil–2–(4–((metilamino)metil)fenetil)benzo[f][1,7]naftiridin–5–amina a partir de 4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzaldehído (del Ejemplo 172/Etapa 1) y metilamina, siguiendo los procedimientos descriptos para el Ejemplo 172, etapa 2. ^{1}H RMN (Acetona– d_6)

Sal de TFA: δ 8,95 (s, 1H), 8,88 (s, 1H), 8,43 (d, 1H), 7,58 (s, 1H), 7,54 (d, 2H), 7,42 (d, 1H), 7,37 (d, 2H), 4,30 (s, 2H), 3,32–3,37 (m, 4H), 2,75 (s, 3H), 2,55 (s, 3H). LRMS [M + H] = 357,2.

Ejemplo 176.

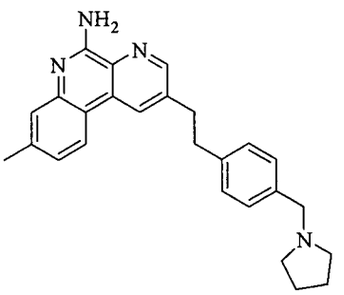
(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)bencilamino)etanol.



Una solución de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzaldehído (del Ejemplo 172/Etapa 1) (1 eq.), etanol amina (8 eq.) y 1 gota de HOAc, disuelta en etanol absoluto (0,018 M) se agitó a 80°C durante 2 horas. La mezcla se enfrió hasta 0°C, y se agregó $NaBH_4$ (3,5 eq.), y la mezcla de reacción se agitó durante otra hora a temperatura ambiente. La mezcla se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la HPLC preparatoria en un sistema de 19 x 50 mm ATLANTIS® de 10 micrones, C 18 (Waters Corp.) usando 10–90% de acetonitrilo (0,035% de TFA) en agua (0,05% de TFA) a fin de lograr un sólido de color amarillo claro en forma de una sal de TFA. ^{1}H RMN (Acetona–d_6) Sal de TFA: δ 8,82 (s, 1H), 8,75 (s, 1H), 8,30 (d, 1H), 7,44 (m, 3H), 7,28(d, 1H), 7,21 (d, 2H), 4,22 (s, 2H), 3,72 (t, 2H), 3,22 (t, 2H), 3,09 (m, 2H), 3,07 (t, 2H), 3,01 (bs, OH), 2,41 (s, 3H). LRMS [M + H] = 387,2.

Ejemplo 177.

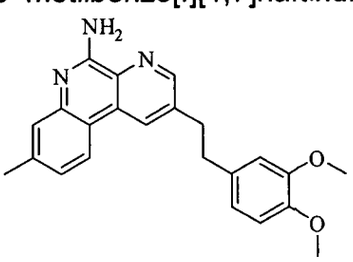
8–Metil–2–(4–(pirrolidin–1–ilmetil)fenetil)benzo[f][1,7]naftiridin–5–amina.



Se preparó 8–metil–2–(4–(pirrolidin–1–ilmetil)fenetil)benzo[f][1,7]naftiridin–5–amina a partir de 4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzaldehído (del Ejemplo 172/Etapa 1) y pirrolidina, siguiendo los procedimientos descriptos para el Ejemplo 172, Etapa 2. ^{1}H RMN (Acetona– d_6) Sal de TFA: δ 8,88 (s, 1H), 8,82 (s, 1H), 8,82 (s, 1H), 8,43 (d, 1H), 8,38 (d, 1H), 7,58 (s, 1H), 7,51 (m, 1H), 7,33 (d, 2H), 4,16 (s, 2H), 3,32–3,38 (m, 4H), 2,55 (s, 3H), 2,20–2,32 (m, 4H), 1,90–1,99 (m, 4H). LRMS [M + H] = 397,2.

Ejemplo 178.

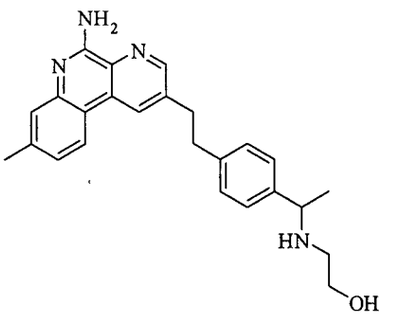
2–(3,4–Dimetoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.



Se preparó 2–(3,4–dimetoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina a partir de 4–etinil–1,2–dimetoxibenceno (comercial), siguiendo los procedimientos descriptos para el Ejemplo 45/Etapas 1 a 3. ^{1}H RMN (Acetona– d_6): δ 8,64 (s, 1H), 8,56 (s, 1H), 8,14 (d, 1H), 7,29 (s, 1H), 7,03 (d, 1H), 6,77 (s, 1H), 6,71 (s, 1H), 6,62 (d, 1H), 6,45 (bs, 2H), 3,62 (s, 6H), 3,12 (t, 2H), 2,94 (t, 2H), 2,33 (s, 3H). LRMS [M + H] = 374,2.

Ejemplo 179.

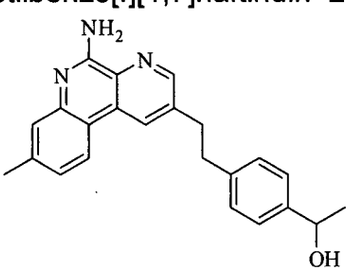
2–(1–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)etanol.



Se preparó 2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)etanol (del Ejemplo 171) a partir de 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona y etanol amina (comercial), siguiendo los procedimientos descriptos para el Ejemplo 176. ^{1}H RMN (Acetona–d_6) de sal de TFA: δ 8,78 (d, 1H), 8,29 (d, 1H), 7,83 (s, 1H), 7,45 (m, 3H), 7,28 (m, 3H), 4,22 (m, 1H), 3,52 (m, 2H), 3,23 (t, 2H), 3,09 (t, 2H), 2,85 (m, 1H), 2,65 (m, 1H), 2,41 (s, 3H), 1,61 (d, 3H). LRMS [M + H] = 401,2.

Ejemplo 180.

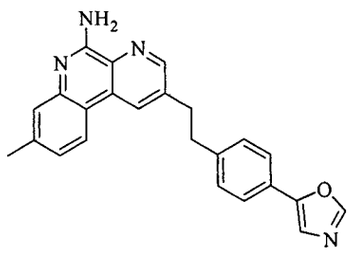
1–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanol.



Se aisló 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanol (del Ejemplo 171) como un producto lateral durante la aminación reductora como se muestra en el Ejemplo 173. ^{1}H RMN (Acetona– d_6) de Sal de TFA: 8,90 (s, 1H), 8,88 (s, 1H), 8,42 (d, 1H), 7,57 (s, 1H), 7,43 (d, 1H), 7,33 (d, 2H), 7,26 (d, 2H), 4,82 (q, 1H), 3,32 (t, 2H), 3,17 (t, 2H), 3,01 2,55 (s, 3H), 1,41 (s, 3H). LRMS [M + H] = 358,2.

Ejemplo 181.

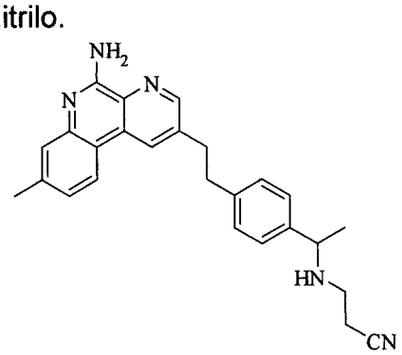
8–Metil–2–(4–(oxazol–5–il)fenetil)benzo[f][1,7]naftiridin–5–amina.



Se preparó 8–metil–2–(4–(oxazol–5–il)fenetil)benzo[f][1,7]naftiridin–5–amina a partir de 5–(4–etinilfenil)oxazol (comercial) siguiendo los procedimientos descriptos para el Ejemplo 45/Etapas 1 a 3. ^{1}H RMN (Acetona– d_6) de Sal de TFA: 8,69 (s, 1H), 8,59 (s, 1H), 8,16 (d, 1H), 8,04 (s, 1H), 7,55 (m, 2H), 7,38 (s, 1H), 7,28 (m, 2H), 7,01 (m, 2H), 3,16 (t, 2H), 3,07 (t, 2H), 2,33 (s, 3H). LRMS [M + H] = 381,2.

Ejemplo 182.

3–(1–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propanonitrilo.

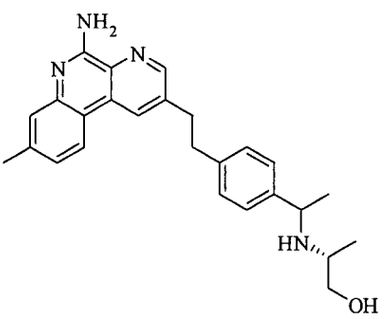


Una solución de 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona (del Ejemplo 171) (1 eq.), 3–aminopropano nitrilo (comercial) (2,5 eq.) disuelta en etanol absoluto (0,014 M) se agitó a 80^{0}C durante 2 horas. La mezcla se enfrió hasta 0^{0}C, y se agregó $NaCNBH_3$ (2 eq.), y la mezcla de reacción se agitó durante otra hora a temperatura ambiente. La mezcla se diluyó con acetato de etilo y cloruro de amonio. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la HPLC

preparatoria en un sistema de 19 x 50 mm ATLANTIS® 10 micrones C18 (Waters Corp.) usando 10–90% de acetonitrilo (0,035% de TFA) en agua (0,05% de TFA) a fin de lograr 3–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propanonitrilo en forma de un sólido de color amarillo claro como una sal de TFA. ^{1}H RMN (Acetona– d_6): δ 8,60 (s, 1H), 8,59 (s, 1H), 8,11 (d, 1H), 7,29 (s, 1H), 7,16 (d, 2H), 7,09 (d, 2H), 7,03 (d, 1H), 6,43 (bs, 2H), 3,65 (m, 1H), 3,12 (t, 2H), 2,99 (t, 2H), 2,56 (m, 2H), 2,35 (m, 2H), 2,32 (s, 3H), 1,16 (d, 3H). LRMS [M + H] = 410,2.

Ejemplo 183.

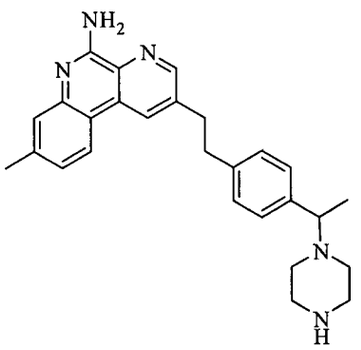
(2R)–2–(1–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propan–1–ol.



Se preparó (2R)–2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propan–1–ol a partir de 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona (del Ejemplo 171) y (R)–2–aminopropan–1–ol (comercial), siguiendo los procedimientos descriptos para el Ejemplo 182. ^{1}H RMN (Acetona– d_6): δ: 8,94 (m, 2H), 8,45 (m, 1H), 7,64 (d, 2H), 7,59 (s, 1H), 7,55 (br s, 2H), 7,41 (m, 3H), 4,65 (m, 1H), 3,81 (m, 1H), 3,35 (t, 2H), 3,25 (t, 2H), 2,56 (s, 3H), 1,73 (m, 3H), 1,29 (d, 3H), 1,23 (d, 3H). LRMS [M + H] = 415,2.

Ejemplo 184.

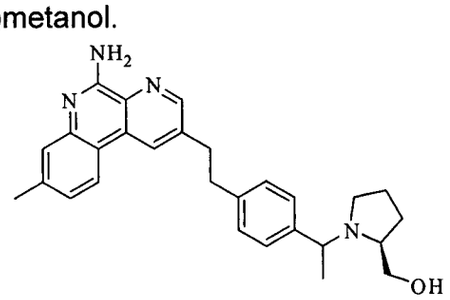
8–Metil–2–(4–(1–(piperazin–1–il)etil)fenetil)benzo[f][1,7]naftiridin–5–amina.



Se preparó 8–metil–2–(4–(1–(piperazin–1–il)etil)fenetil)benzo[f][1,7]naftiridin–5–amina a partir de 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona (del Ejemplo 171) y piperazina (comercial), siguiendo los procedimientos descriptos para el Ejemplo 182. ^{1}H RMN (Metanol– d_4) Sal de TFA: δ 8,83 (s, 1H), 8,75 (s, 1H), 8,39 (d, 1H), 7,51 (s, 1H), 7,46 (d, 1H), 7,26 (m, 4H), 3,62 (m, 1H), 3,25 (t, 2H), 3,12 (t, 2H), 2,80 (m, 4H), 2,69 (m, 4H), 2,56 (s, 3H), 1,42 (d, 3H). LRMS [M + H] = 426,2.

Ejemplo 185.

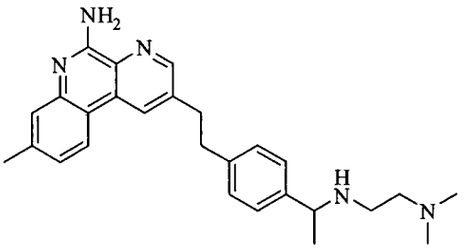
((2S)–1–(1–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidin–2–il)metanol.



Se preparó ((2S)–1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidin–2–il)metanol a partir de 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona (del Ejemplo 171) y (S)–pirrolidin–2–ilmetanol (comercial), siguiendo los procedimientos descriptos para el Ejemplo 182. ^{1}H RMN (Acetona– d_6) Sal de TFA: δ 8,83 (s, 1H), 8,80 (s, 1H), 8,43 (d, 1H), 7,36–7,53 (m, 6H), 4,68 (m, 1H), 3,69 (m, 2H), 3,19–3,21 (m, 4H), 2,55 (m, 4H), 1,75–1,78 (m, 6H), 1,74 (d, 3H). LRMS [M + H] = 441,2.

Ejemplo 186.

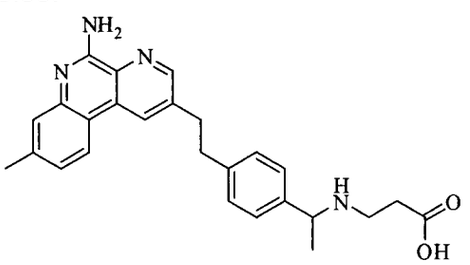
N^1–(1–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^2,N^2–dimetiletano–1,2–diamina.



N^1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^2,N^2–dimetiletano–1,2–diamina se preparó a partir de 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona (del Ejemplo 171) y N^1,N^1–dimetiletano–1,2–diamina (comercial), siguiendo los procedimientos descriptos para el Ejemplo 182. ^{1}H RMN (Acetona– d_6) Sal de TFA: δ 8,85 (m, 2H), 8,43 (d, 1H), 7,52 (s, 1H), 7,48 (m, 2H), 7,40 (m, 2H), 6,69 (m, 1H), 4,39 (m, 1H), 3,42 (m, 2H), 3,18–3,25 (m, 6H), 2,87 (s, 6H), 2,56 (s, 3H), 1,69 (d, 3H). LRMS [M + H] = 428,2.

Ejemplo 187.

Ácido 3–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propanoico.

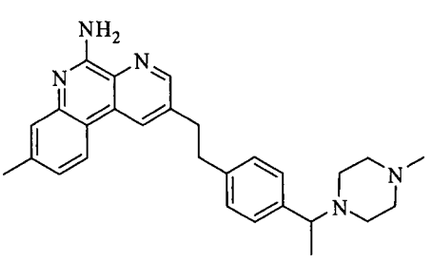


Una solución de 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona (del Ejemplo 171) (1 eq.), ácido 3–aminopropanoico (comercial) (5 eq.), trietilamina (3 eq.) disuelta en etanol absoluto (0,042 M) se agitó a 50°C durante 3 horas. La mezcla se enfrió hasta 0°C, y se agregó $NaCNBH_3$ (1 eq.), y la mezcla de reacción se agitó durante otras seis horas a temperatura ambiente. A continuación, se agregó otro equivalente de $NaCNBH_3$, y

la mezcla de reacción se agitó a 50°C durante otra hora. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo y cloruro de amonio saturado. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la HPLC preparatoria en un sistema de 19 x 50 mm ATLANTIS® 10 micrones C18 (Waters Corp.) usando 10–90% de acetonitrilo (0,035% de TFA) en agua (0,05% de TFA), a fin de lograr ácido 3–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propanoico en forma de un sólido de color blanco como una sal de TFA. ^{1}H RMN (Metanol– d_4) Sal de TFA: δ 8,74 (s, 1H), 8,42 (d, 1H), 7,66 (m, 2H), 7,50 (m, 1H), 7,31 (d, 2H), 7,23 (m, 2H), 4,24 (m, 1H), 3,21 (t, 2H), 3,14 (t, 2H), 2,75–3,10 (m, 2H), 2,51 (t, 2H), 2,10 (s, 3H), 1,55 (d, 3H). LRMS [M + H] = 429,2.

Ejemplo 188.

8–Metil–2–(4–(1–(4–metilpiperazin–1–il)etil)fenetil)benzo[f][1,7]naftiridin–5–amina.

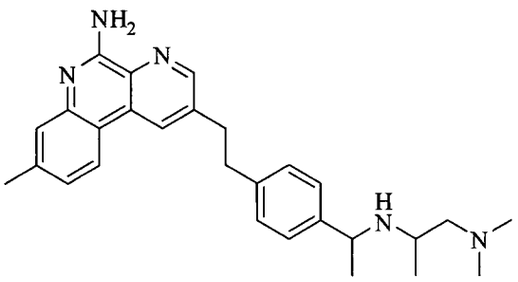


Se preparó 8–metil–2–(4–(1–(4–metilpiperazin–1–il)etil)fenetil)benzo[f][1,7]naftiridin–5–amina a partir de 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona (del Ejemplo 171) y 1–metilpiperazina (comercial), siguiendo los procedimientos descriptos para el Ejemplo 182. ^{1}H RMN (Acetona– d_6) Sal de TFA: δ 8,84 (s, 1H), 8,80 (s, 1H), 8,41 (d, 1H), 7,52 (s, 1H), 7,42–7,46 (m, 3H), 7,36–7,38 (m, 2H), 3,53 (m, 1H), 3,18 (m,

2H), 3,12 (m, 2H), 2,92 (s, 2H), 2,66 (s, 2H), 2,56 (s, 2H), 2,16 (s, 3H), 1,99 (m, 2H), 1,69 (d, 3H), 1,30 (s, 3H). LRMS [M + H] = 440,2.

Ejemplo 189.

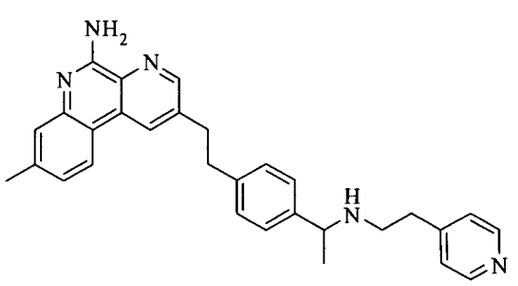
N^2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^1,N^1–dimetilpropano–1,2–diamina.



Se preparó N^2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^1,N^1–dimetilpropano–1,2–diamina a partir de 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona (del Ejemplo 171) y N^1,N^1–dimetilpropano–1,2–diamina (comercial) siguiendo los procedimientos descriptos para el Ejemplo 182. ^{1}H RMN (Acetona– d_6) Sal de TFA: δ 8,83 (m, 2H), 8,40 (d, 1H), 7,46–7,51 (m, 3H), 7,43 (m, 1H), 7,37 (d, 2H), 4,54 (m, 1H), 3,74 (m, 1H), 3,19 (m, 4H), 2,90 (s, 3H), 2,77 (s, 3H), 2,55 (s, 3H), 2,41 (d, 2H), 1,66 (d, 3H), 1,39 (d, 3H). LRMS [M + H] = 442,2.

Ejemplo 190.

8–Metil–2–(4–(1–(2–(piridin–4–il)etilamino)etil)fenetil)benzo[f][1,7]naftiridin–5–amina.

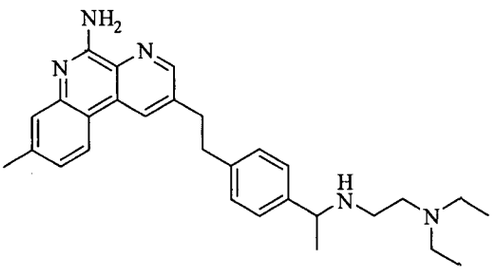


Se preparó 8–metil–2–(4–(1–(2–(piridin–4–il)etilamino)etil)fenetil)benzo[f][1,7]naftiridin–5–amina a partir de 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona (del Ejemplo 171) y 2–

(piridin–4–il)etanamina (comercial) siguiendo los procedimientos descriptos para el Ejemplo 182. ^{1}H RMN (Acetona– d_6) Sal de TFA: δ 8,94 (m, 2H), 8,92 (d, 2H), 8,73 (s, 1H), 8,43 (d, 1H), 7,60 (m, 2H), 7,40 (m, 2H), 7,16–7,26 (m, 3H), 4,55 (m, 1H), 3,55 (m, 4H), 2,56 (m, 4H), 2,12 (s, 3H), 1,73 (d, 3H). LRMS [M + H] = 462,2.

Ejemplo 191.

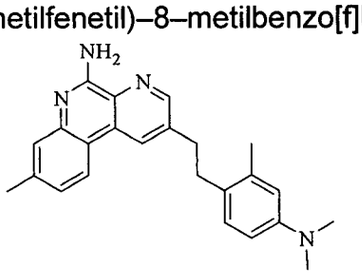
N^1–(1–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^2,N^2–dietiletano–1,2–diamina.



Se preparó N^1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^2,N^2–dietiletano–1,2–diamina a partir de 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona (del Ejemplo 171) y N^1,N^1–dietiletano–1,2–diamina (comercial) siguiendo los procedimientos descriptos para el Ejemplo 182. ^{1}H RMN (Acetona– d_6) Sal de TFA: δ: 8,81 (s, 1H), 8,75 (s, 1H), 8,23 (d, 1H), 7,60 (d, 2H), 7,39 (d, 2H), 7,28 (m, 2H), 4,51 (m, 1H), 3,82 (m, 1H), 3,62 (m, 1H), 3,34 (m, 4H), 3,20 (t, 2H), 2,46 (s, 3H), 2,10 (m, 4H), 1,74 (d, 3H), 1,34 (t, 6H). LRMS [M + H] = 456,2.

Ejemplo 192.

2–(4–(Dimetilamino)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina



Etapa 1: 4–yodo–N,N,3–trimetilanilina.

Una solución de 4–yodo–3–metilanilina (comercial) (1 eq.), $NaHCO_3$ (2,5 eq.) y yodometano (2,5 eq.), en DMF (0,2 M), se agitó a temperatura ambiente durante la noche. La mezcla de reacción luego se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la fase acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio, y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, y se aisló 4–yodo–N,N,3–trimetilanilina en forma de un sólido de color amarillo.

Etapa 2: Síntesis de: N,N,3–trimetil–4–((trimetilsilil)etinil)anilina.

Una solución de 4–yodo–*N,N*–3–trimetilanilina (de la etapa previa) (1 eq.), etiniltrimetilsilano (1,5 eq.), diclorobis(trifenilfosfina)–paladio (II) (20% en moles), yoduro de cobre (20% en moles) y trietilamina (0,4 M) se agitó a temperatura ambiente durante la noche. La mezcla de reacción luego se diluyó con acetato de etilo y solución de cloruro de amonio. Se separaron las dos fases, y la fase acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio, y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–100% de acetato de etilo en hexano, y se aisló N,N,3–trimetil–4–((trimetilsilil)etinil)anilina en forma de un sólido de color amarillo.

Etapa 3: 4–etinil–N,N,3–trimetilanilina.

Una solución de *N,N*–3–trimetil–4–((trimetilsilil)etinil)anilina (de la etapa previa) (1 eq.), K_2CO_3 (2,5 eq.), en MeOH ((0,15 M) se agitó a temperatura ambiente durante 6 horas. Los sólidos se separaron mediante la filtración, y el líquido se concentró al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80%

de acetato de etilo en hexano, y se aisló 4–etinil–*N,N*–3–trimetilanilina en forma de un sólido de color amarillo.

Etapa 4: 3–cloro–5–((4–(dimetilamino)–2–metilfenil)etinil) picolinonitrilo.

Una solución de 4–etinil–*N,N*–3–trimetilanilina (de la etapa previa) (1 eq.) 3,5–dicloropicolinonitrilo (1,2 eq.), diclorobis(trifenilfosfina)–paladio (II) (10% en moles), yoduro de cobre (10% en moles) y DMF:trietilamina (0,28 M) se agitó a temperatura ambiente durante la noche. La mezcla de reacción luego se diluyó con acetato de etilo y solución de cloruro de amonio. Se separaron las dos fases, y la fase acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio, y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–100% de acetato de etilo en hexano, y se aisló 3–cloro–5–((4–(dimetilamino)–2–metilfenil)etinil) picolinonitrilo en forma de un sólido amarillento.

Etapa 5: 2–((4–(dimetilamino)–2–metilfenil)etinil)–8–metilbenzo[f] [1,7] naftiridin–5–amina.

Una solución de ter–butil 5–metil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenilcarbamato (1,3 eq.) y 3–cloro–5–((4–(dimetilamino)–2–metilfenil)etinil) picolinonitrilo (de la etapa previa) (1,0 eq.), tetraquis(trifenil–fosfina)paladio (10% en moles) y solución acuosa de carbonato de sodio, 2 N (2,0 eq.), en tolueno/etanol (2:1, 0,17 M) se agitó a 100°C durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con metanol. Los sólidos insolubles se separaron mediante la filtración, y el filtrado se concentró al vacío de modo de obtener un residuo bruto. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr 2–((4–

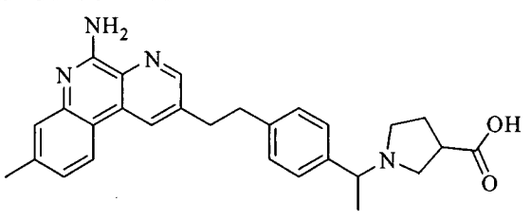
(dimetilamino)–2–metilfenil)etinil)–8–metilbenzo[f] [1,7] naftiridin–5–amina en forma de un sólido de color amarillo,

Etapa 6: 2–(4–(dimetilamino)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

A una solución de 2–((4–(dimetilamino)–2–metilfenil)etinil)–8–metilbenzo[f][1,7]naftiridin–5–amina (1 eq.), (de la etapa previa) en acetato de etilo/etanol (1:5, 0,035 M) se agregó 10% en peso de paladio sobre carbón (0,2 eq.). Se introdujo gas hidrógeno por medio de un balón, y la reacción se agitó durante 3,5 horas. La mezcla se filtró a través de una almohadilla de celite, lavando con diclorometano. El filtrado se concentró al vacío y se purificó por HPLC preparatoria en un sistema de 19 x 50 mm ATLANTIS® 10 micrones C18 (Waters Corp.) usando 10–90% de acetonitrilo (0,035% TFA) en agua (0,05% TFA), a fin de lograr 2–(4–(dimetilamino)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina como un sólido de color blanco en forma de una sal de TFA. ^{1}H RMN (Acetona– d_6) Sal de TFA: δ 8,81 (s, 1H), 8,74 (s, 1H), 8,34 (d, 1H), 7,89 (s, 1H), 7,47 (m, 2H), 7,38 (m, 2H), 3,34 (s, 6H), 3,32 (t, 2H), 3,28 (t, 2H), 2,57 (s, 3H), 2,34 (s, 3H). LRMS [M + H] = 371,2.

Ejemplo 193.

Ácido 1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidina–3–carboxílico.

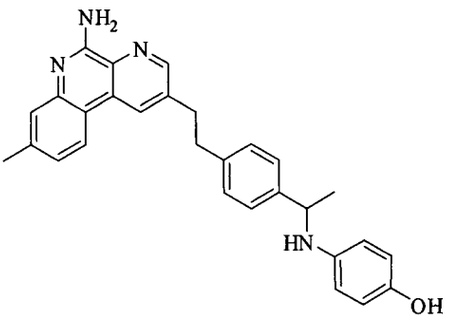


Se preparó ácido 1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidina–3–carboxílico a partir de 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona (del Ejemplo 171) y ácido pirrolidina–3–carboxílico (comercial), siguiendo los procedimientos descriptos para

el Ejemplo 187, excepto que, en este caso, se usó ácido acético en lugar de la trietilamina (30%). ^{1}H RMN (Acetona– d_6) Sal de TFA: δ 8,81 (s, 1H), 8,75 (s, 1H), 8,70 (s, 1H), 8,28 (d, 1H), 7,59 (d, 2H), 7,37 (m, 3H), 4,46 (m, 1H), 4,21 (m 1H), 3,45 (m, 2H), 3,32 (m, 2H), 3,21 (m, 2H), 3,17 (m, 2H), 2,27 (m, 2H), 2,07 (s, 3H) 1,77 (d, 3H). LRMS [M + H] = 455,2.

Ejemplo 194.

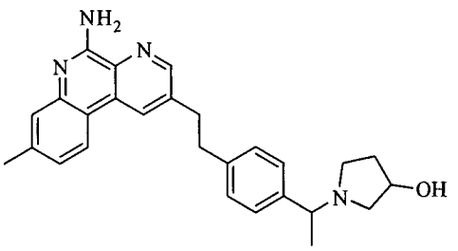
4–(1–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)fenol.



Se preparó 4–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)fenol a partir de 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona (del Ejemplo 171) y 4–aminofenol, siguiendo los procedimientos descriptos para el Ejemplo 187, excepto que, en este caso, se usó ácido acético en lugar de trietilamina (28%). ^{1}H RMN (Acetona– d_6) Sal de TFA: δ 8,83 (s, 1H), 8,73 (s, 1H), 8,33 (d, 1H), 7,44 (s, 1H), 7,40 (d, 2H), 7,36 (d, 1H), 7,24 (d, 2H), 7,10 (d, 2H), 6,76 (d, 2H), 4,72 (m, 1H) 3,27 (t, 2H), 3,12 (t, 2H), 2,50 (s, 3H), 2,06 (d, 3H). LRMS [M + H] = 449,2.

Ejemplo 195.

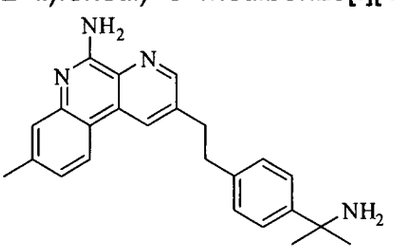
1–(1–(4–(2–(5–Amino–8–metilbenzo[f][1,7]naftiridin–2 il)etil)fenil)etil)pirrolidin–3–ol.



Se preparó 1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2 il)etil)fenil)etil)pirrolidin–3–ol a partir de 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona (del Ejemplo 171) y pirrolidin–3–ol, siguiendo los procedimientos descriptos para el Ejemplo 187, excepto que, en este caso, se usó ácido acético en lugar de trietilamina (20%). ^{1}H RMN (Acetona–d_6) Sal de TFA: δ 8,83 (s, 1H), 8,76 (s, 1H), 8,72 (s, 1H), 8,29 (d, 1H), 7,57 (s, 1H), 7,42 (s, 1H), 7,33–7,38 (m, 3H), 4,41(m, 2H), 3,77 (m, 2H), 3,33 (t, 2H), 3,21 (t, 2H), 3,19 (m, 2H), 3,10 (m, 2H), 2,10 (s, 3H), 1,75 (d, 3H). LRMS [M + H] = 427,2.

Ejemplo 196.

2–(4–(2–Aminopropan–2–il)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

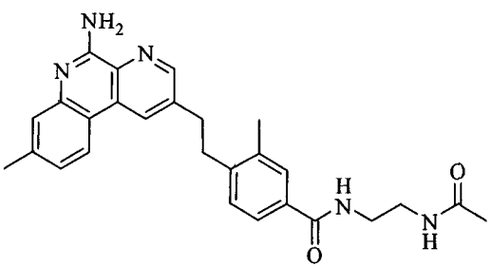


A una solución de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzonitrilo (del Ejemplo 64, etapa 1) (1 eq.), disuelta en THF seco (0,029 M) se agregó, muy lentamente, bromuro de metil magnesio (6 eq.), y la mezcla de reacción se agitó a temperatura ambiente durante media hora. A continuación, se agregó al matraz de reacción tetra–isopropóxido de titanio (3 eq.) en un período de tiempo de diez minutos. La mezcla de reacción se sometió a reflujo durante 16 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo y cloruro de amonio saturado. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro

y se concentraron al vacío. El material bruto se purificó por medio de la HPLC preparatoria en un sistema de 19 x 50 mm ATLANTIS® 10 micrones C18 (Waters Corp.), usando 10–90% de acetonitrilo (0,035% de TFA) en agua (0,05% de TFA) a fin de lograr 2–(4–(2–aminopropan–2–il)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina como un sólido de color blanco, de la sal de TFA. ^{1}H RMN (Metanol– d_4) Sal de TFA δ: 9,01 (s, 2H), 8,92 (s, 1H), 8,42 (s, 1H), 7,65 (d, 2H), 7,56 (s, 1H), 7,39 (m, 2H), 3,19 (m, 4H), 2,54 (s, 3H), 1,82 (6H). LRMS [M + H] = 371,2.

Ejemplo 197.

N–(2–Acetamidoetil)–4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamida.

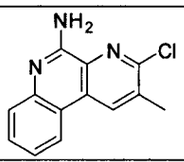
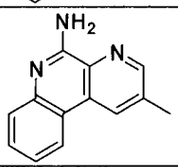
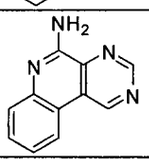
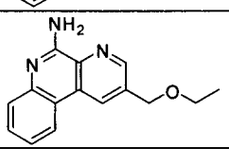
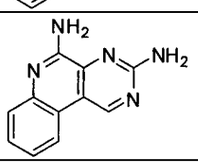
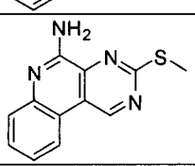
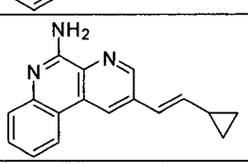
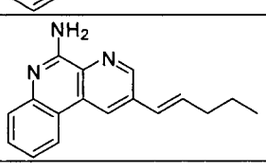


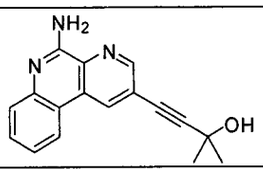
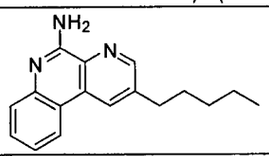
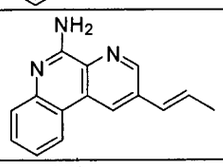
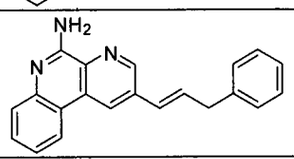
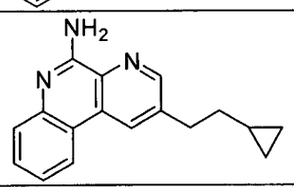
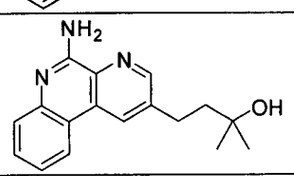
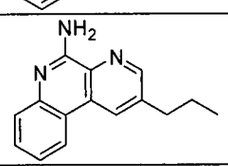
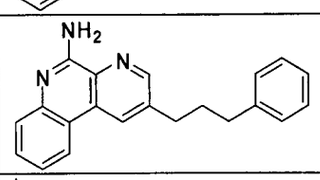
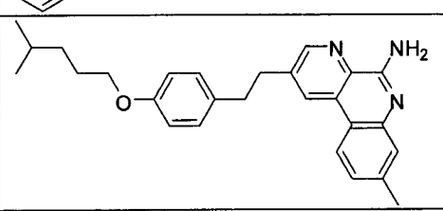
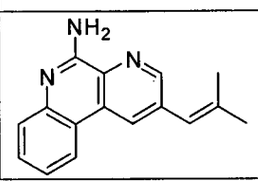
A una solución de cloruro de 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoílo (Ejemplo 116/Etapa 2) y trietilamina (2,5 eq.) en éter (0,05 M) se agregó N–(2–aminoetil)acetamida (5,0 eq.). La mezcla de reacción se agitó durante la noche. A continuación, la mezcla de reacción se diluyó con acetato de etilo y agua. Se separaron las dos fases, y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío. El material bruto se purificó por medio de la cromatografía instantánea en un sistema COMBIFLASH® (ISCO) usando 0–80% de acetato de etilo en hexano, a fin de lograr N–(2–acetamidoetil)–4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamida como un sólido de color blanco. ^{1}H RMN ($CDCl_3$): δ 8,61 (s, 1H), 8,38 (s, 1H), 8,07 (d, 1H), 7,65 (s, 1H), 7,51–7,56 (m, 2H), 7,10–7,16 (m,

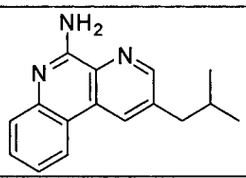
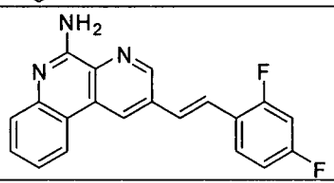
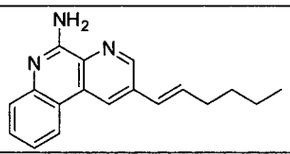
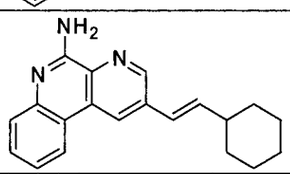
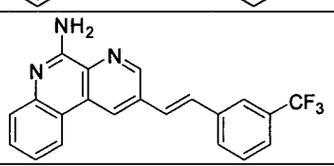
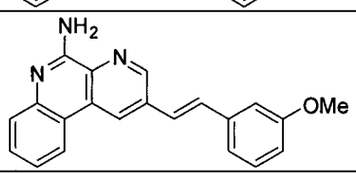
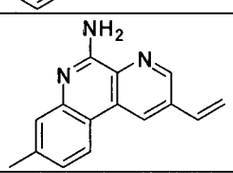
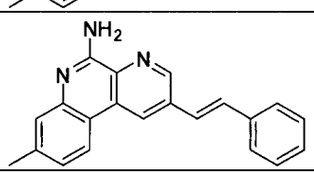
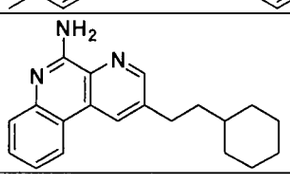
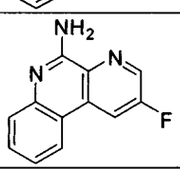
2H), 6,25 (br, 2H), 3,50–3,59 (m, 4H), 3,08–3,16 (m, 4H), 2,62 (s, 3H), 2,52 (s, 3H), 2,35(s, 3H). LRMS [M + H] = 455,2.

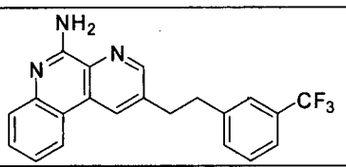
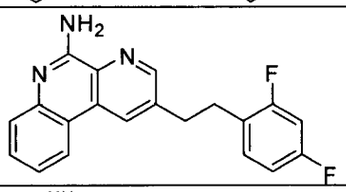
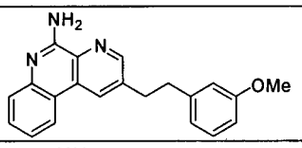
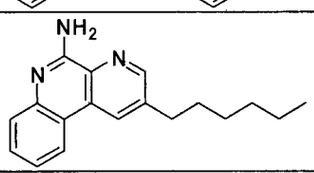
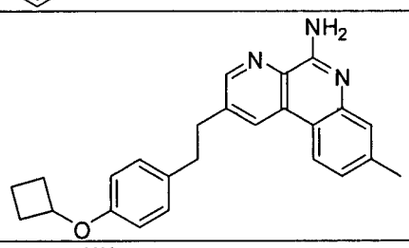
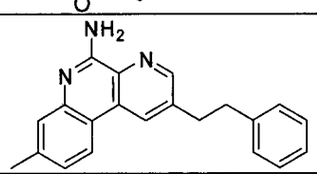
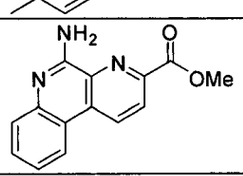
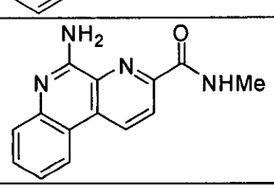
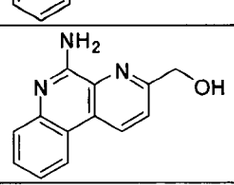
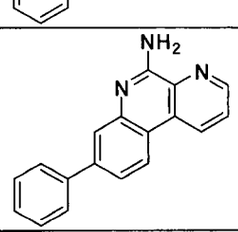
Compuestos representativos adicionales de la Fórmula (I), preparados siguiendo los procedimientos que se describen anteriormente, se exponen en la Tabla 1.

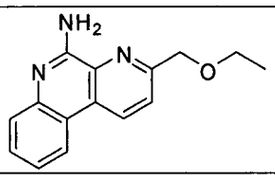
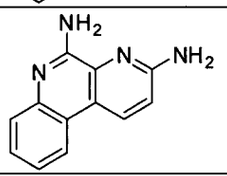
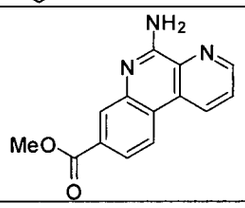
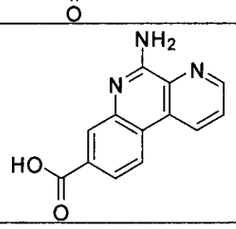
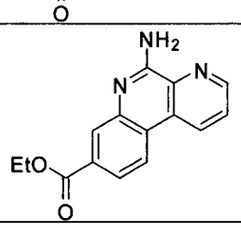
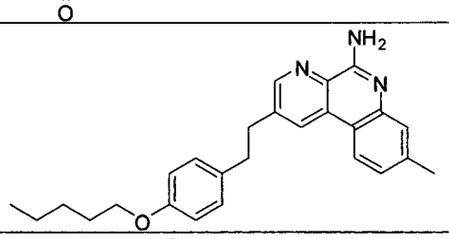
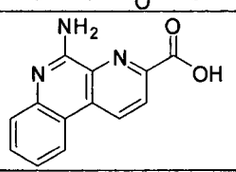
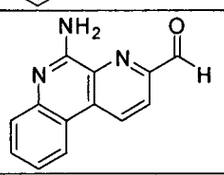
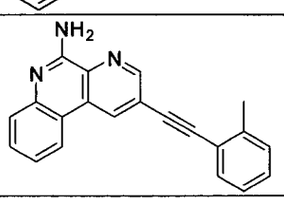
Tabla 1.

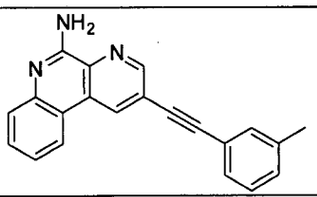
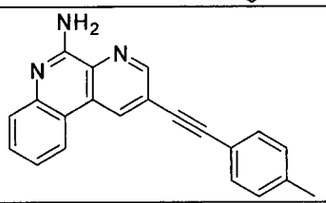
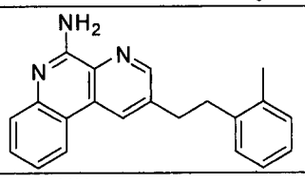
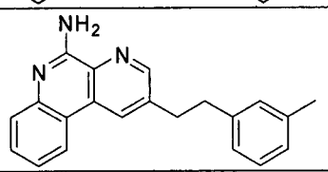
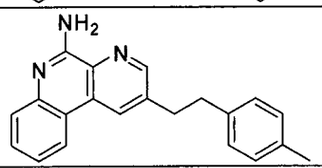
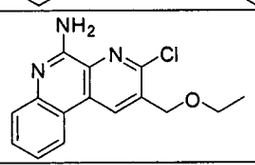
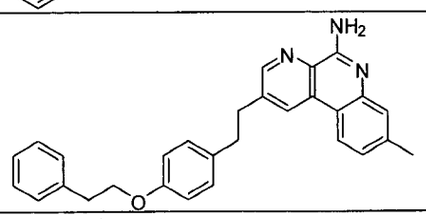
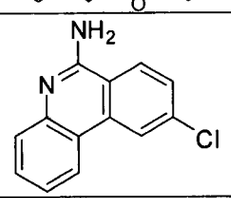
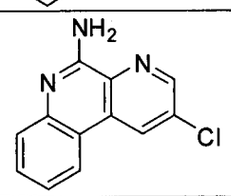
Compuesto Número	**Estructura**	**Información física MS (m/z) [M + H]**
1		244,0
2		210,2
3		197,1
4		254,1
5		212,1
6		243,1
7		262,1
8		264,1

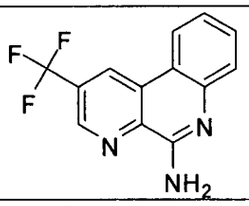
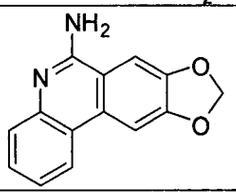
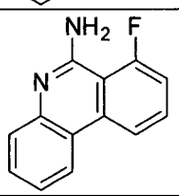
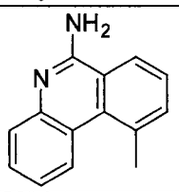
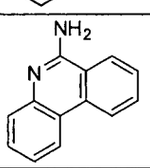
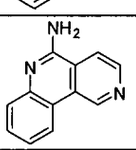
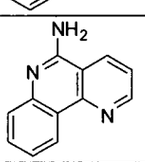
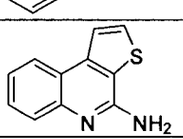
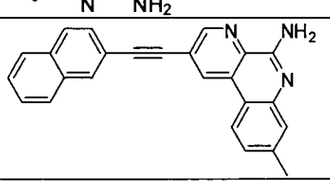
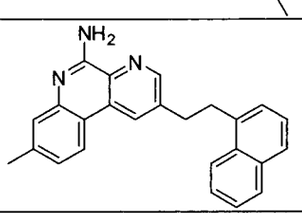
9		278,1
10		266,2
11		236,2
12		312,1
13		264,1
14		282,1
15		238,2
16		314,2
17		414,2
18		250,1

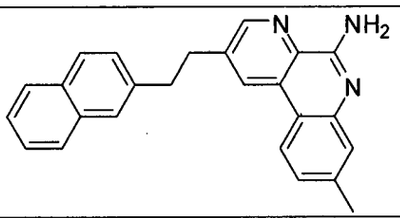
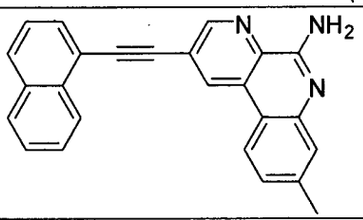
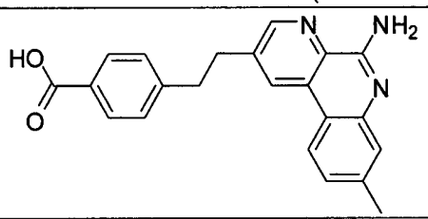
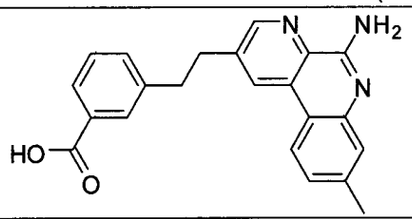
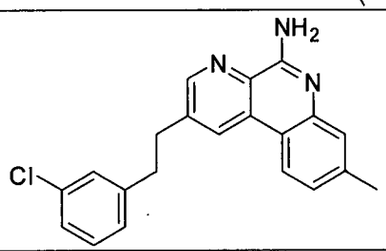
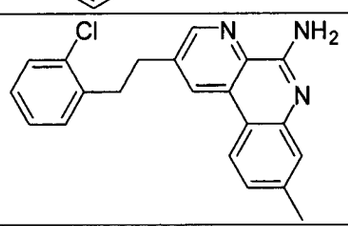
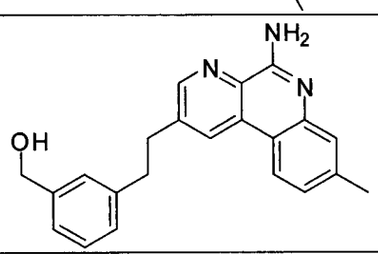
19		252,1
20		334,1
21		278,2
22		304,2
23		366,2
24		328,2
25		236,1
26		312,2
27		306,1
28		214,0

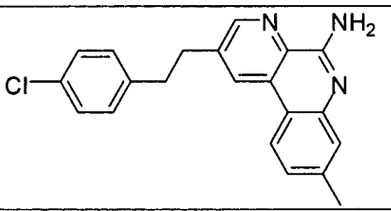
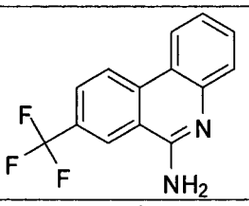
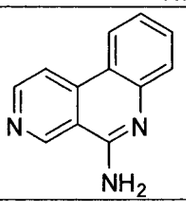
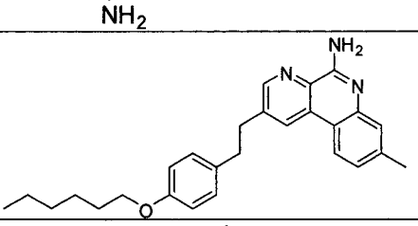
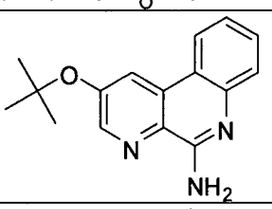
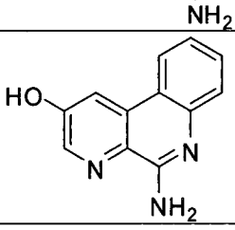
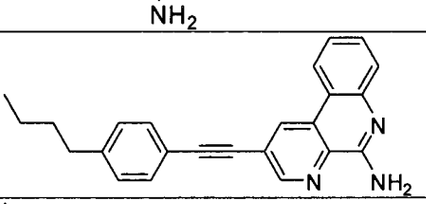
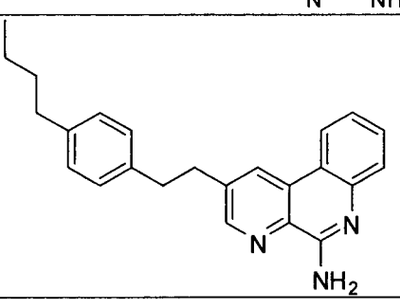
29		368,1
30		336,1
31		330,2
32		280,2
33		384,2
34		314,2
35		254,1
36		253,1
37		226,1
38		272,1

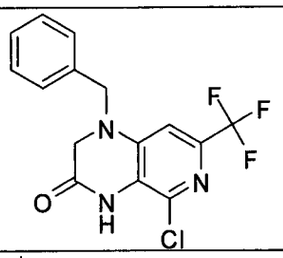
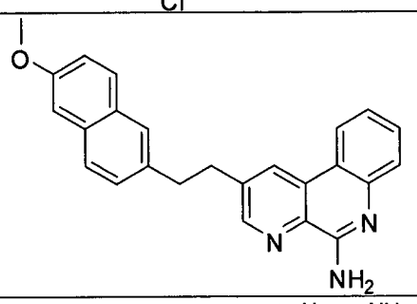
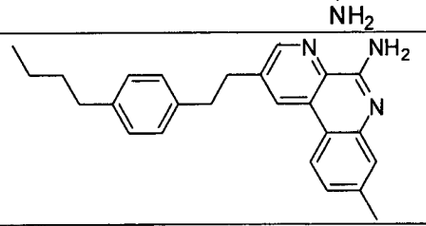
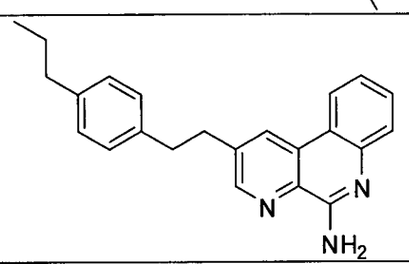
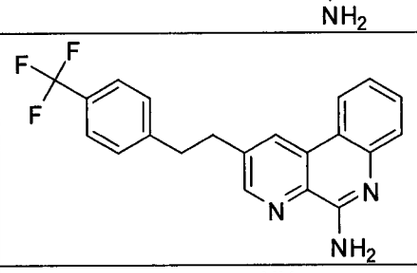
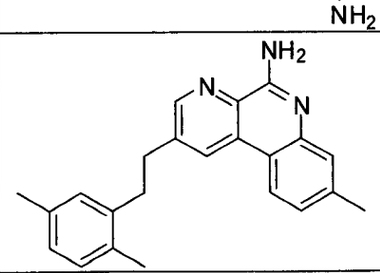
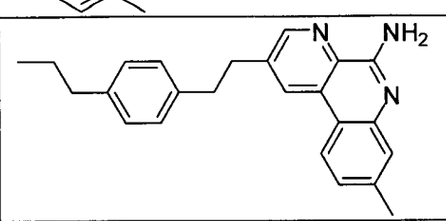
39		254,1
40		211,1
41		254,1
42		240,1
43		268,1
44		400,2
45		240,1
46		224,1
47		310,1

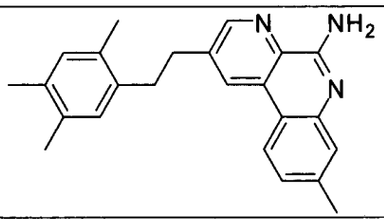
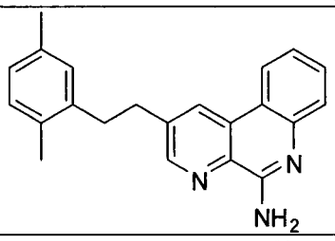
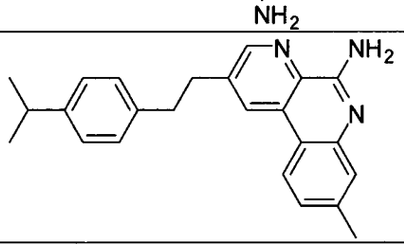
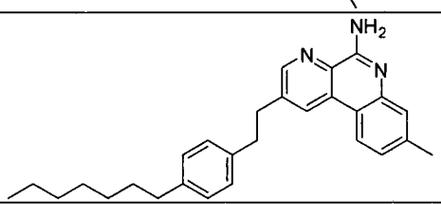
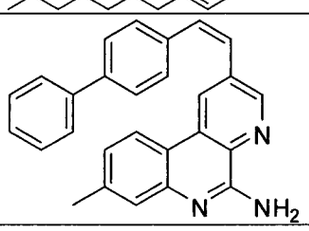
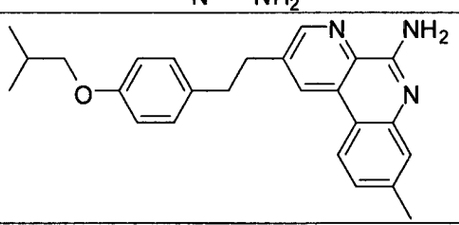
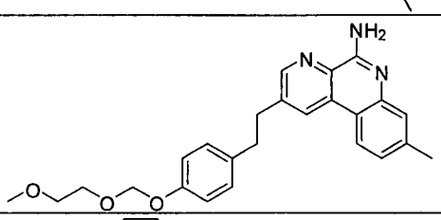
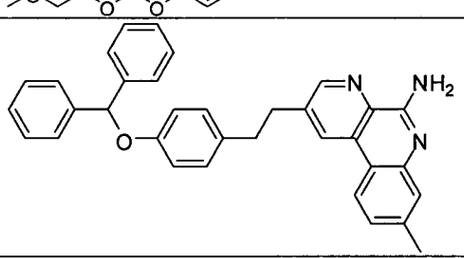
48		310,1
49		310,1
50		314,2
51		314,2
52		314,2
53		288,1
54		434,2
55		229,1
56		230,0

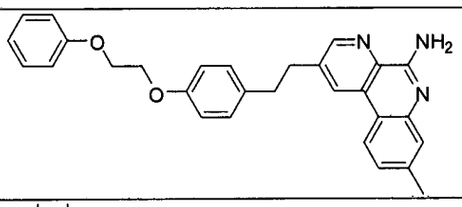
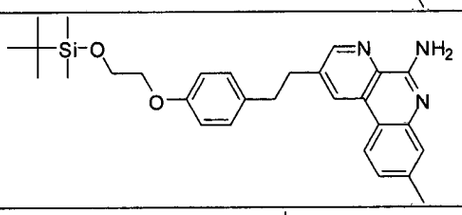
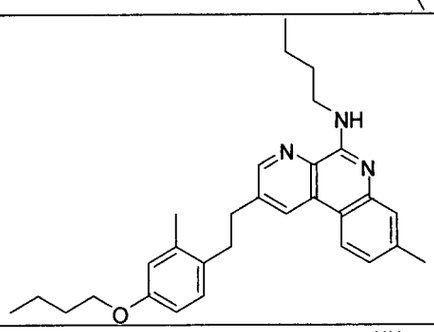
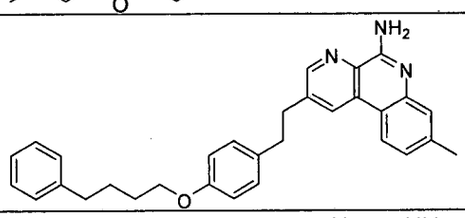
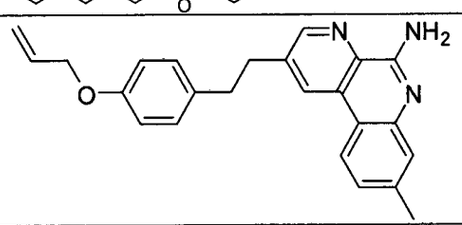
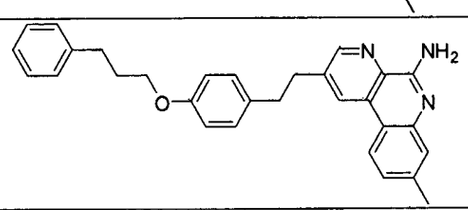
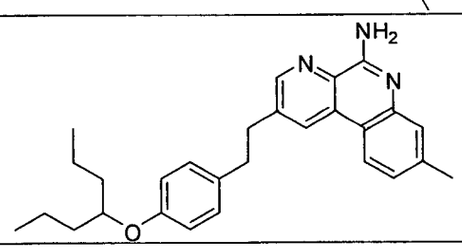
57		264,1
58		239,1
59		213,1
60		209,1
61		195,1
62		196,1
63		196,1
64		201,2
65		360,1
66		364,5

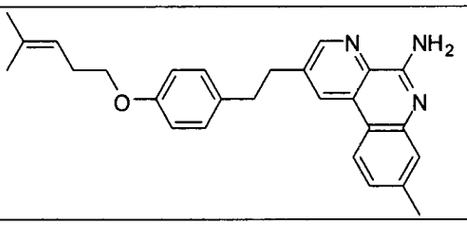
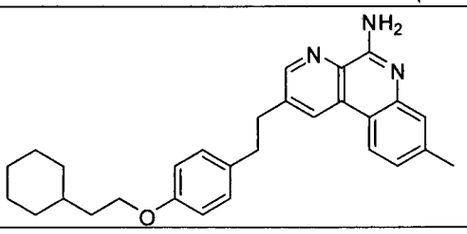
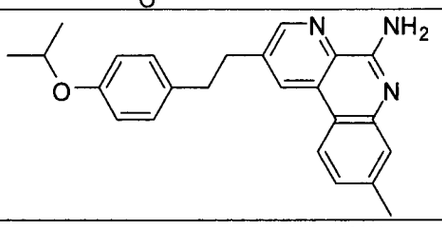
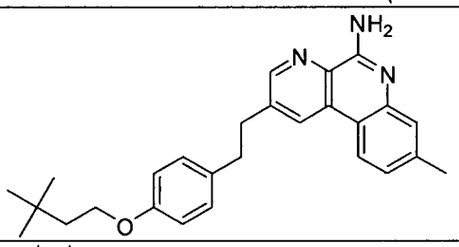
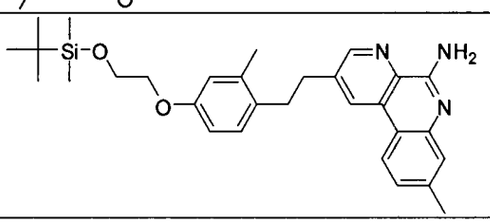
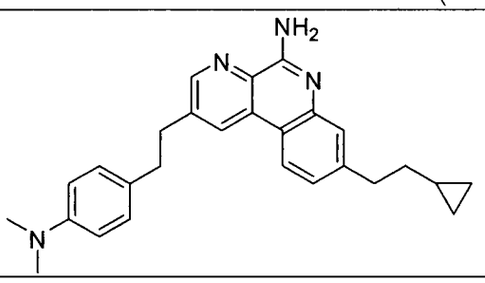
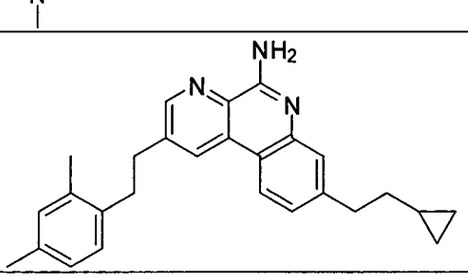
67		364,5
68		360,1
69		358,4
70		358,4
71		348,8
72		348,8
73		344,4

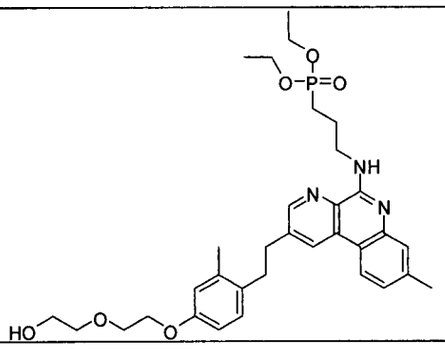
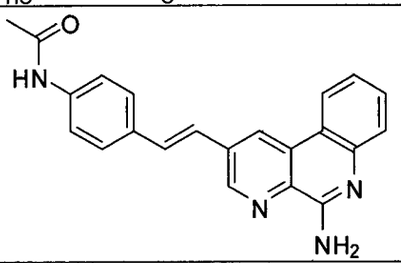
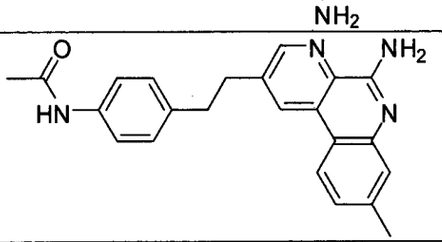
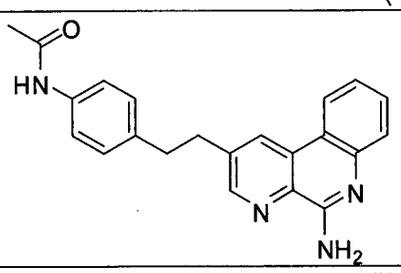
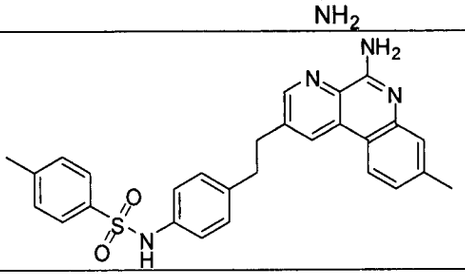
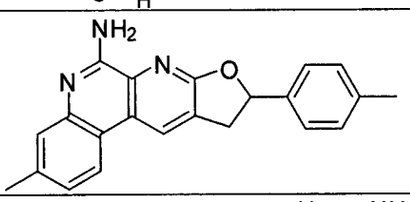
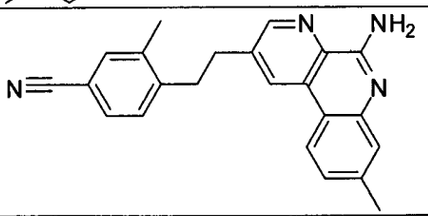
74		348,8
75		263,0
76		196,0
77		414,3
78		268,1
79		212,0
80		352,1
81		356,2

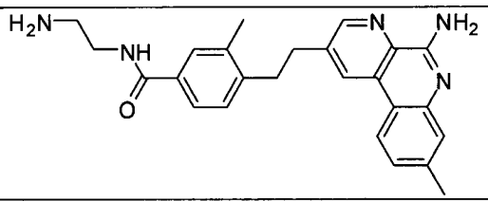
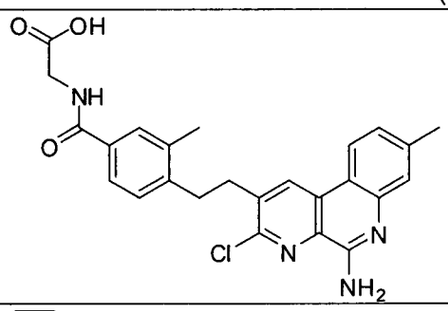
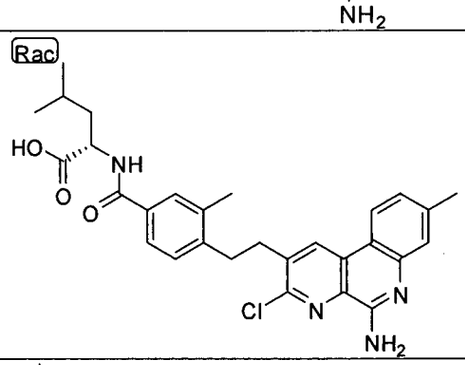
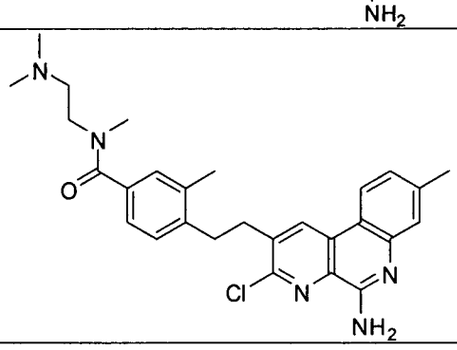
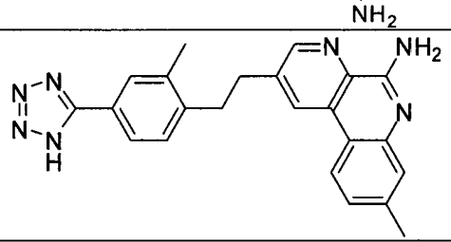
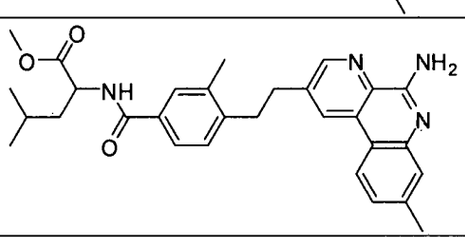
82		341,0
83		380,1
84		370,2
85		342,1
86		368,1
87		342,1
88		356,2

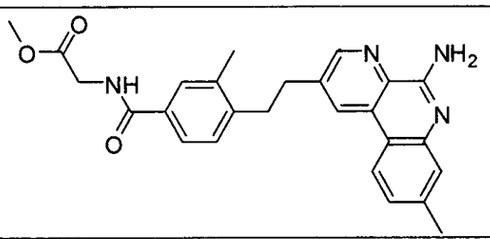
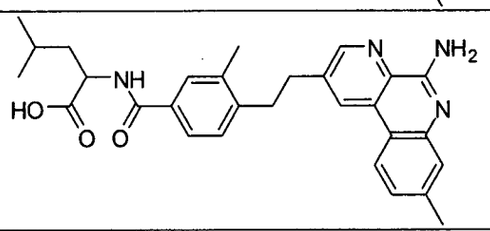
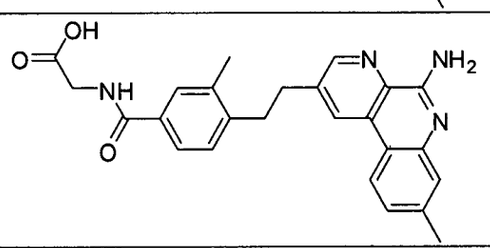
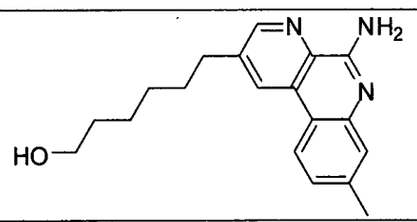
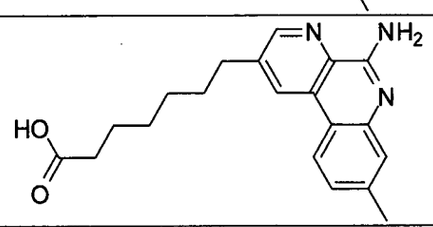
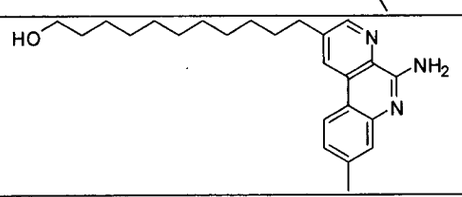
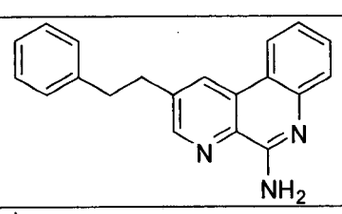
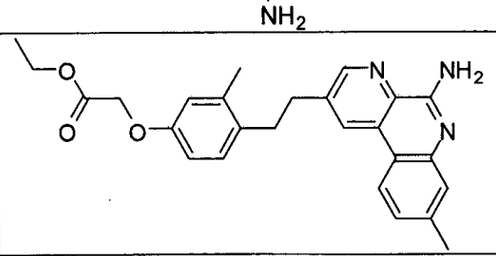
89		356,2
90		328,1
91		356,2
92		412,2
93		388,1
94		386,2
95		418,2
96		496,2

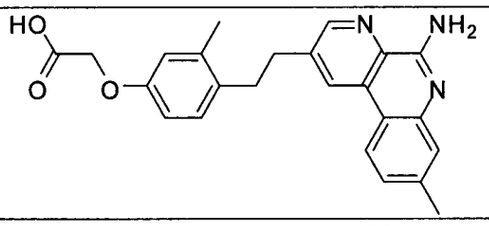
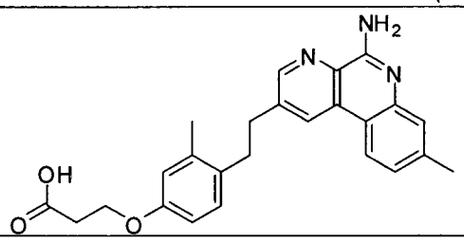
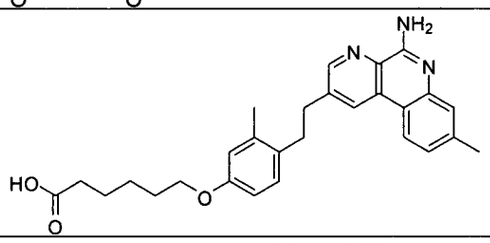
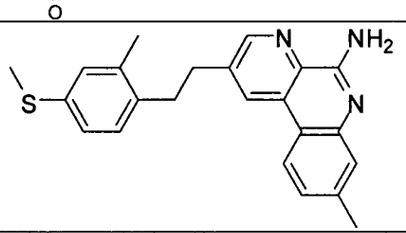
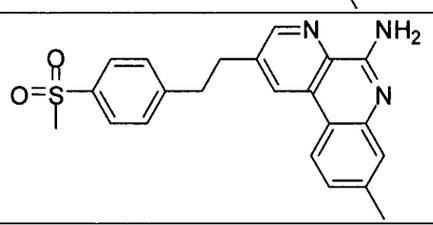
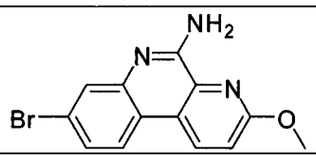
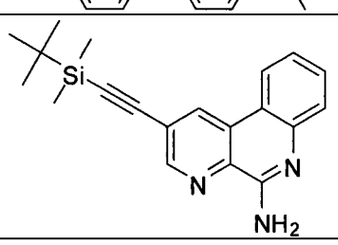
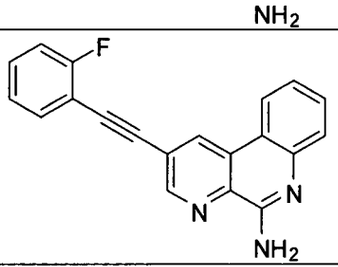
97		450,2
98		488,2
99		456,3
100		462,3
101		370,2
102		448,6
103		428,3

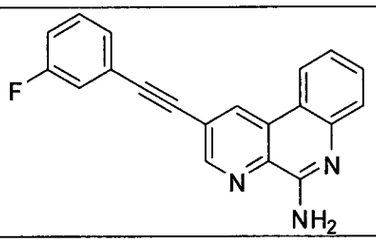
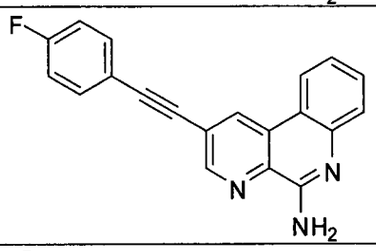
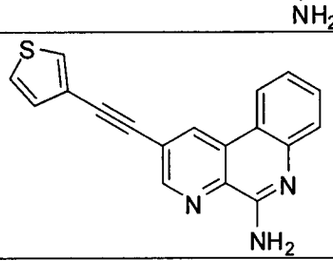
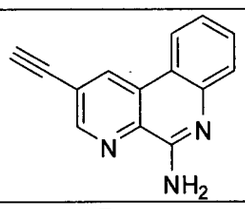
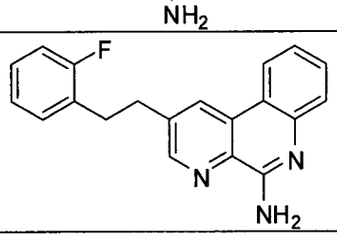
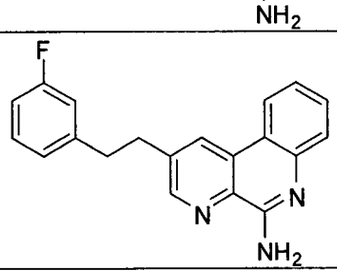
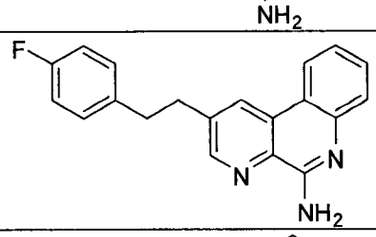
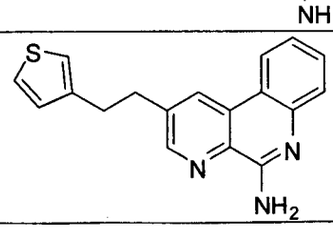
104		412,2
105		440,3
106		372,2
107		414,3
108		502,3
109		411,3
110		396,2

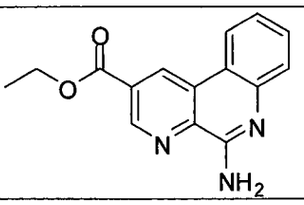
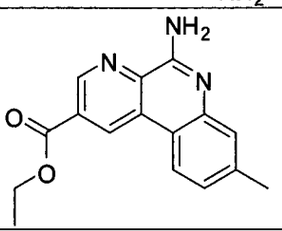
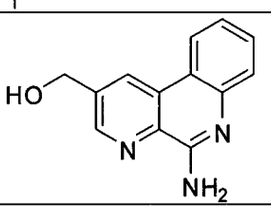
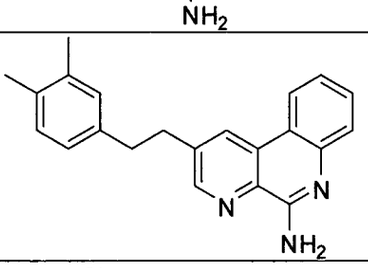
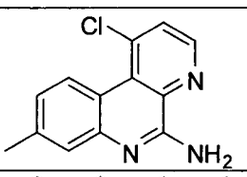
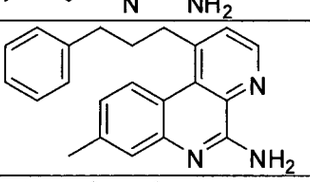
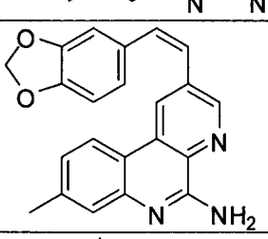
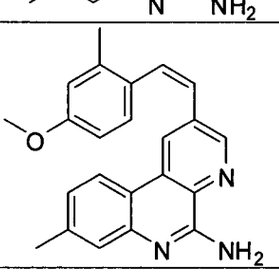
111		610,3
112		355,2
113		371,2
114		357,2
115		483,2
116		342,2
117		353,2

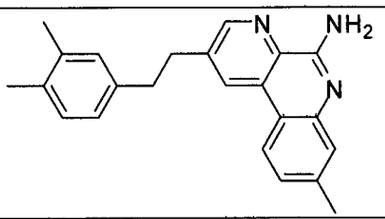
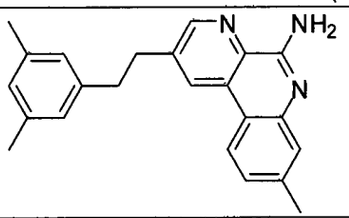
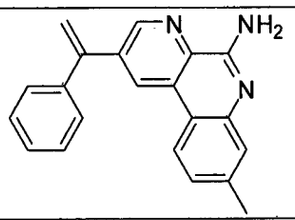
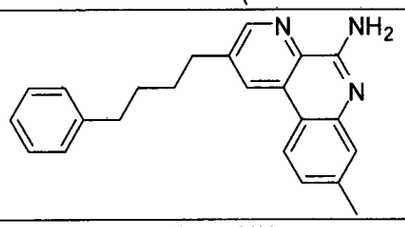
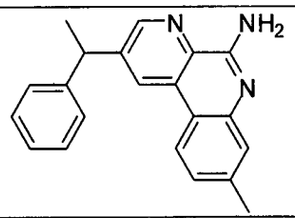
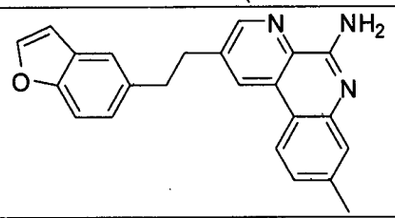
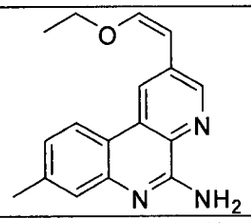
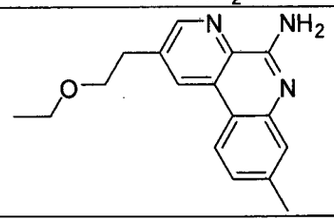
118		414,2
119		463,2
120		519,2
121		490,2
122		396,2
123		499,3

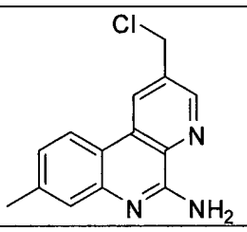
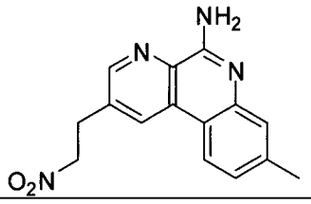
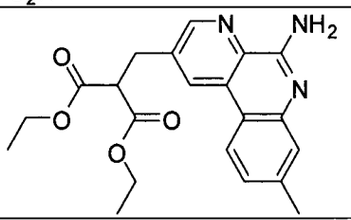
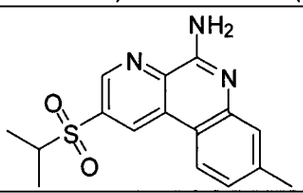
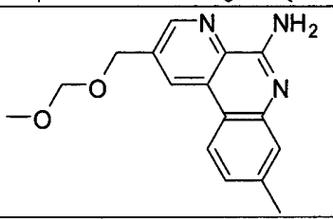
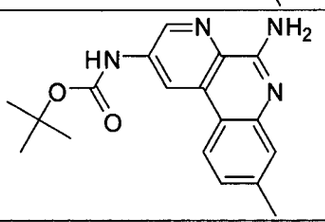
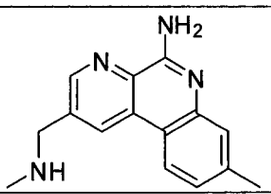
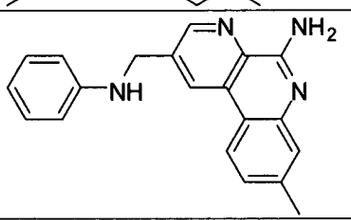
124		443,2
125		485,3
126		429,2
127		310,2
128		338,2
129		380,3
130		300,1
131		430,2

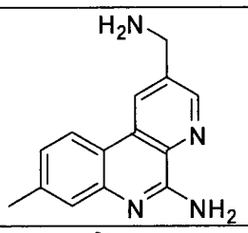
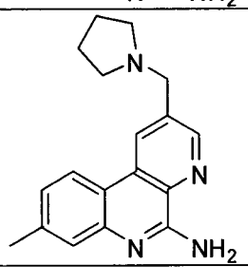
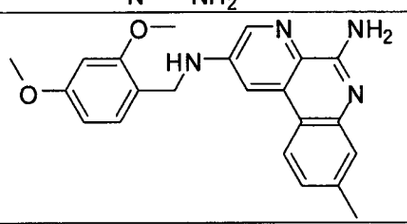
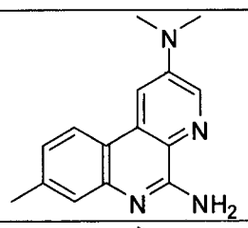
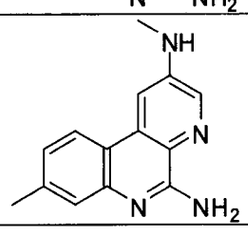
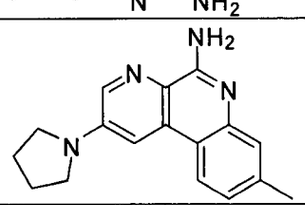
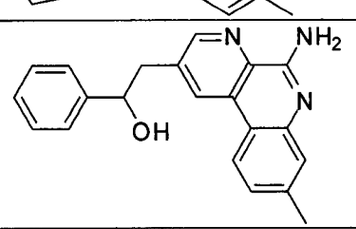
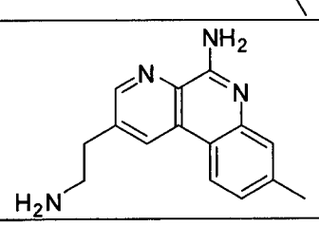
132		402,2
133		416,2
134		458,2
135		374,2
136		392,1
137		304,0
138		334,2
139		314,1

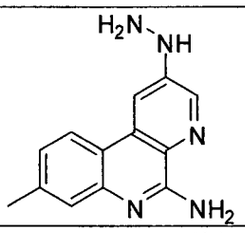
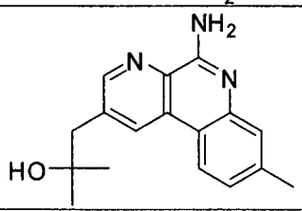
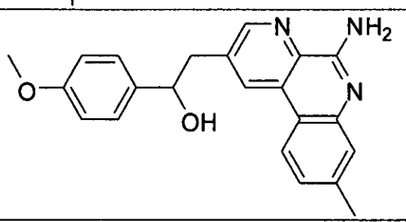
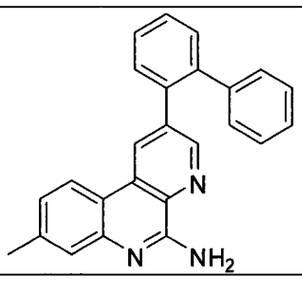
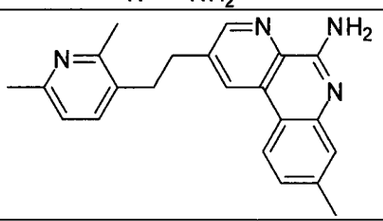
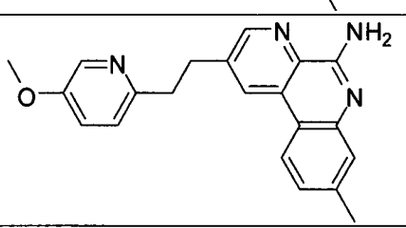
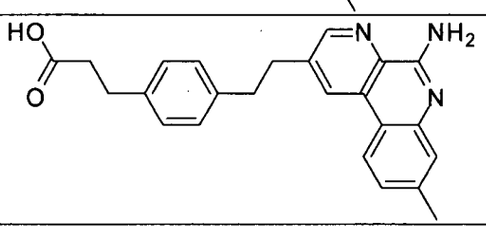
140		314,1
141		314,1
142		302,1
143		220,1
144		318,1
145		318,1
146		318,1
147		306,1

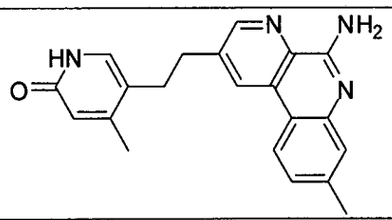
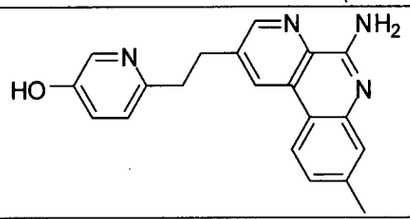
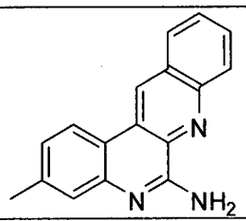
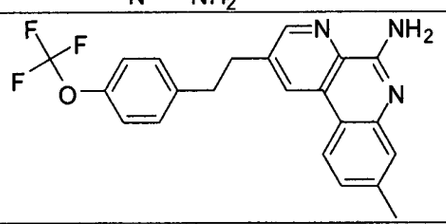
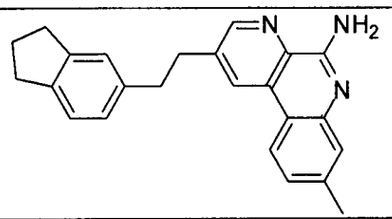
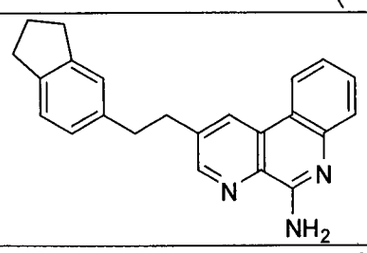
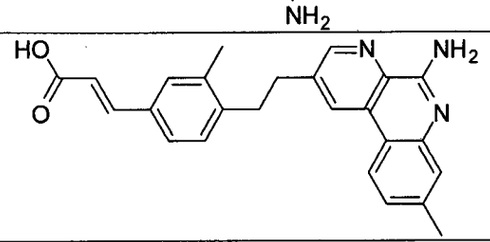
148		268,1
149		282,1
150		226,1
151		328,2
152		244,1
153		328,2
154		356,1
155		356,2

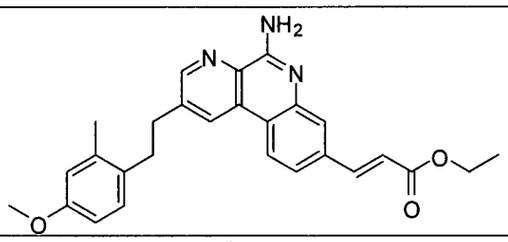
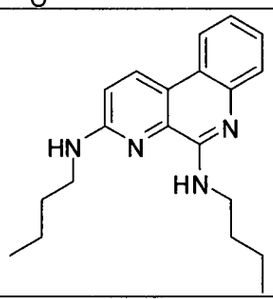
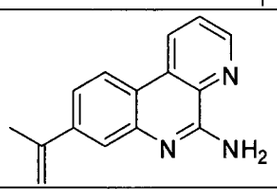
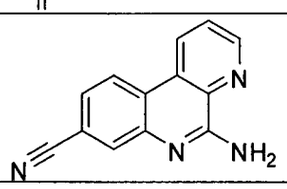
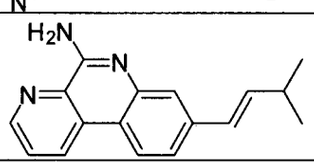
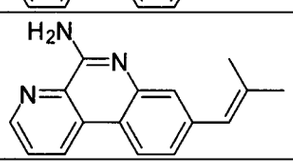
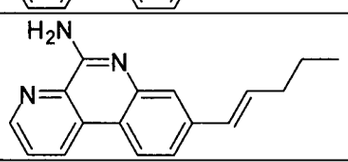
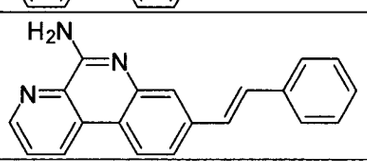
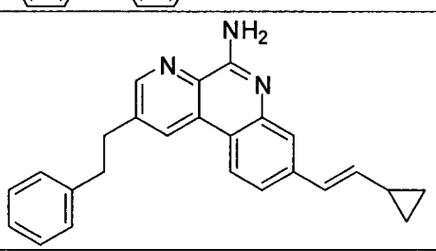
156		342,2
157		342,2
158		312,1
159		342,2
160		314,2
161		353,2
162		280,1
163		282,2

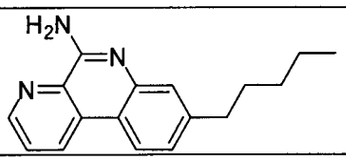
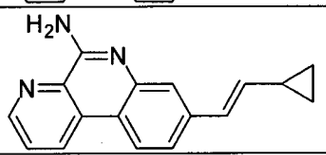
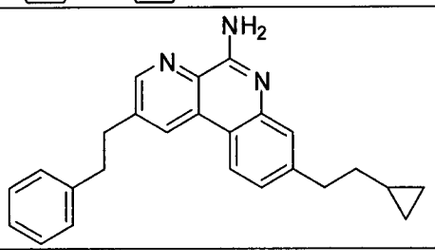
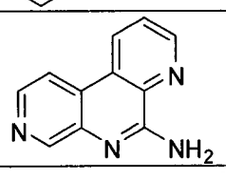
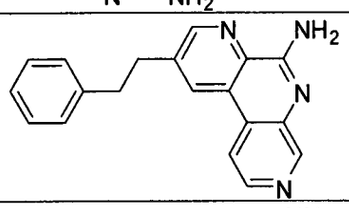
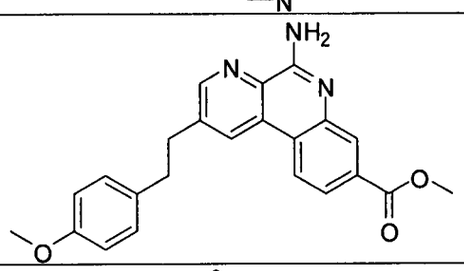
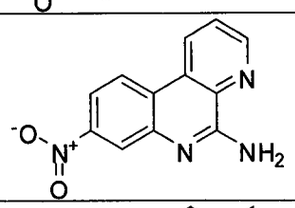
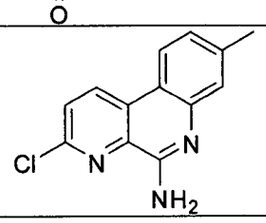
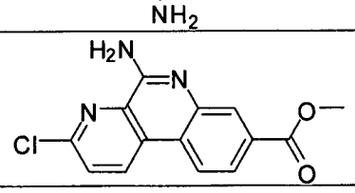
164		258,1
165		283,1
166		382,2
167		316,1
168		284,1
169		325,2
170		253,1
171		315,2

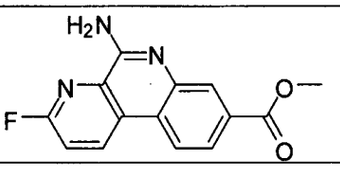
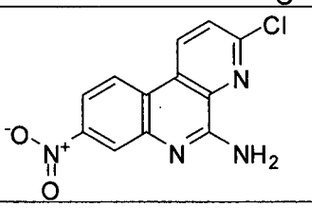
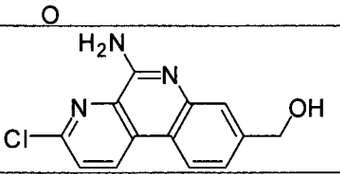
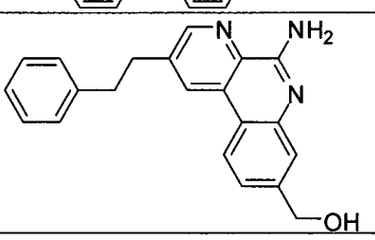
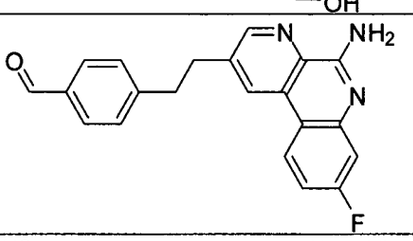
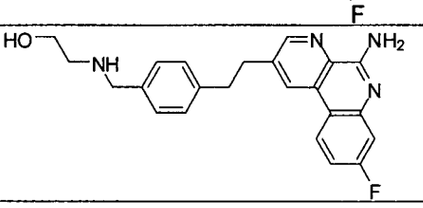
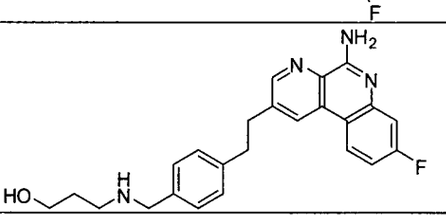
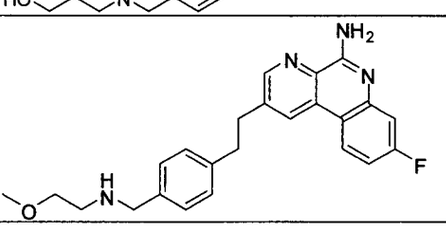
172		239,1
173		293,2
174		375,2
175		253,1
176		239,1
177		279,2
178		330,2
179		253,1

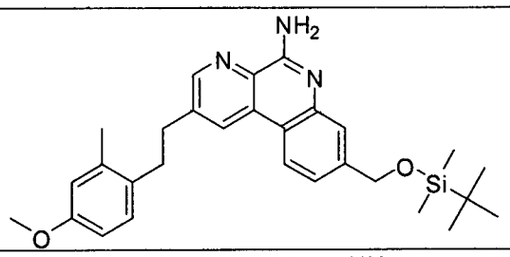
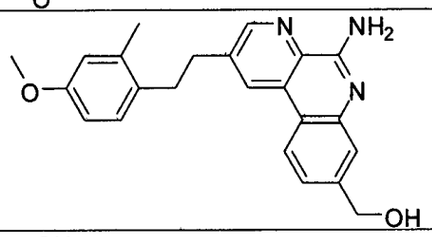
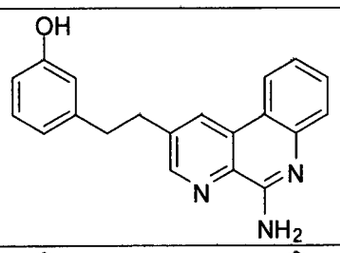
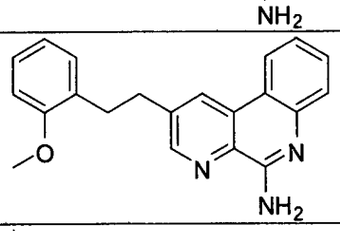
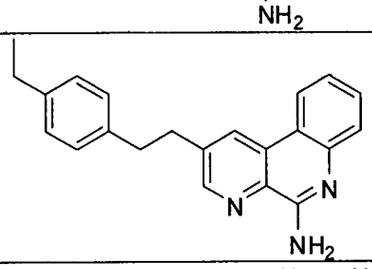
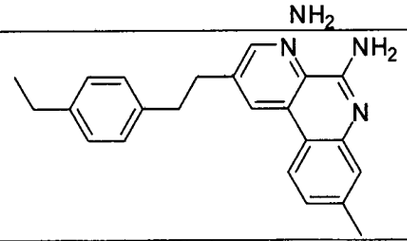
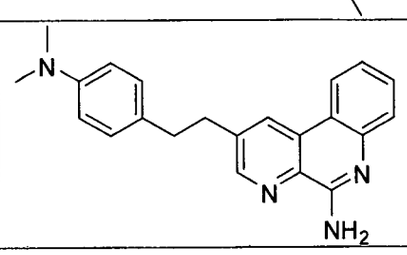
180		240,1
181		282,2
182		360,2
183		362,2
184		343,2
185		345,2
186		386,2

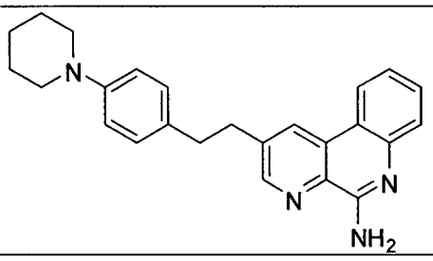
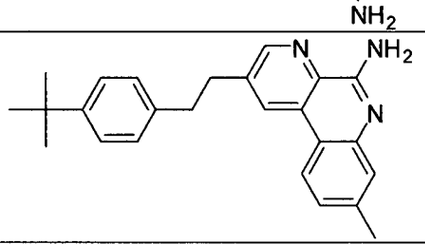
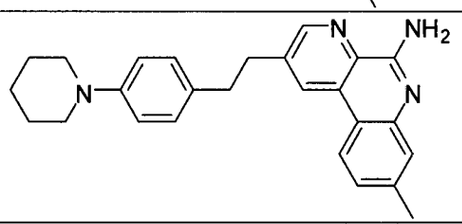
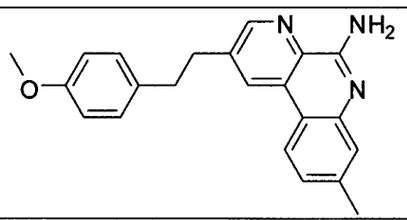
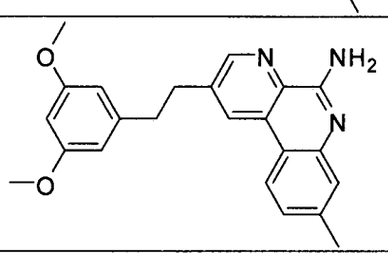
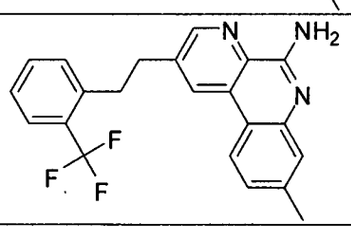
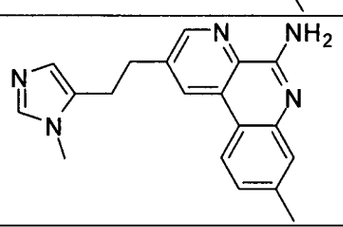
187		345,2
188		331,1
189		260,1
190		398,1
191		354,2
192		340,2
193		398,2

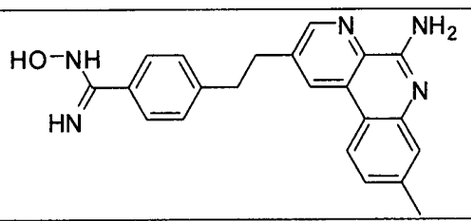
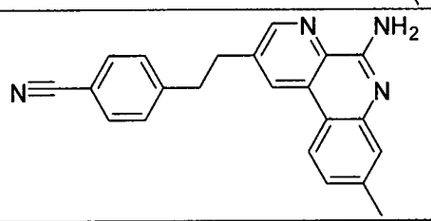
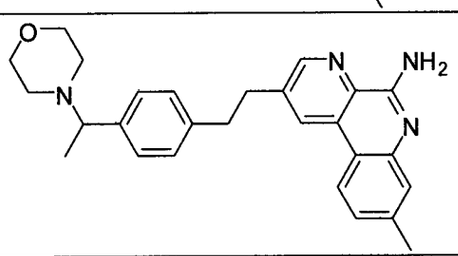
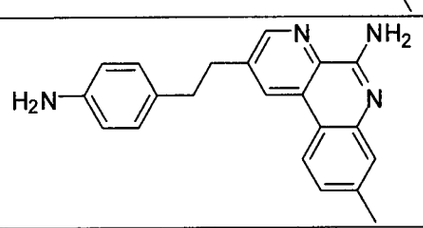
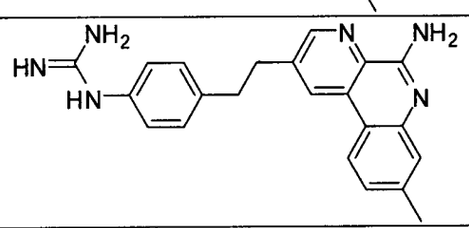
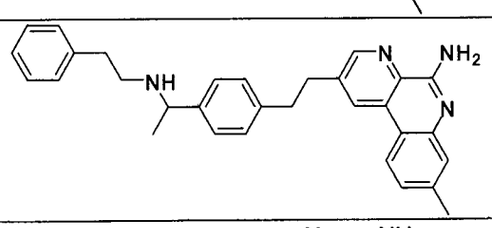
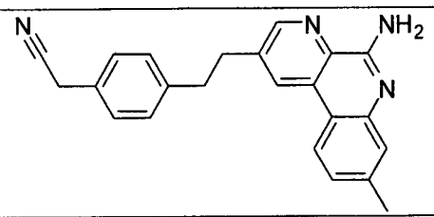
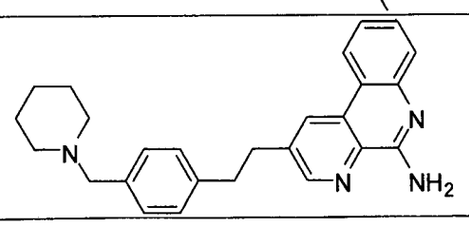
194		442,2
195		323,2
196		236,1
197		221,1
198		264,1
199		250,1
200		264,1
201		298,1
202		366,2

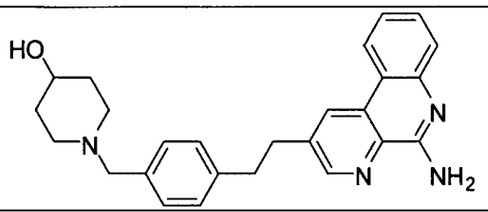
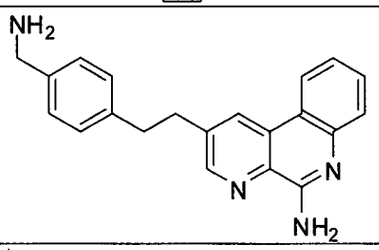
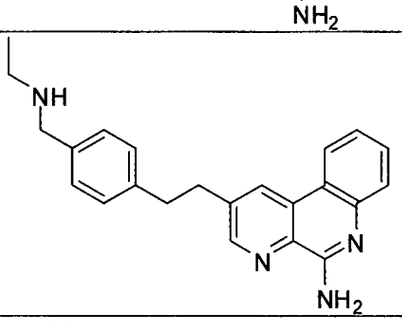
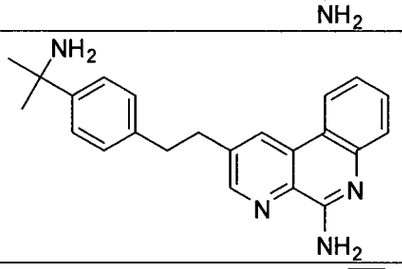
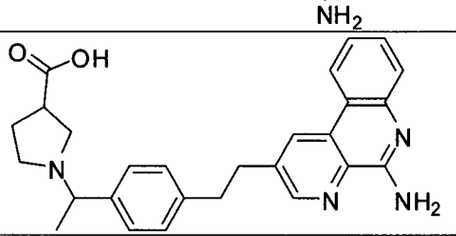
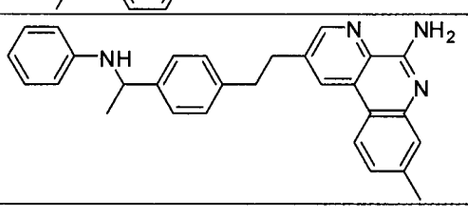
203		266,2
204		262,1
205		368,2
206		197,1
207		301,1
208		388,2
209		241,1
210		244,1
211		288,1

212		272,1
213		275,0
214		260,1
215		330,2
216		346,1
217		391,2
218		405,2
219		405,2

220		488,3
221		374,2
222		316,2
223		330,2
224		328,2
225		342,2
226		343,2

227		383,2
228		370,2
229		397,2
230		344,2
231		374,2
232		382,2
233		318,2

234		372,2
235		339,2
236		427,2
237		329,2
238		371,2
239		461,3
240		353,2
241		411,2

242		427,2
243		443,2
244		371,2
245		357,2
246		441,2
247		433,2

Ejemplo 198.

Eficacia *in vivo* de los compuestos en la mejoría de la respuesta inmunitaria.

Con el objetivo de demostrar la capacidad de los compuestos revelados en la presente solicitud para mejorar la respuesta inmunitaria a un antígeno

bacteriano, cuando se administran a un sujeto con el antígeno, se usaron tres compuestos en conjunto con una vacuna serogrupo B de *N. meningitidis* recombinada. La vacuna, que se describe en forma más completa en la referencia de Giuliani *et al.* (2006): *Proc. Natl. Acad. Sci. U. S. A.*, 103 (29): 10834–9 y en el documento WO 2004/032958 –denominada, en esta solicitud, "3MenB," se ensayó *in vivo* en ratones, ya sea con MF59, ya sea con MF59 + uno de los compuestos descriptos en esta solicitud. Los ratones se inmunizaron con dos dosis administradas en forma intramuscular con 3MenB/MF59 + uno de seis de los compuestos, o, como un control positivo, una cantidad de un oligonucleótido CpG ("CpG"), R848, o Imiquimod (ImiQ). Se comparó además un control positivo adicional de 3MenB/MF59 + OMV (vesículas de membrana externa derivadas de la cepa de serogrupo B de *N. meningitidis* NZ98/254). La valoración del anticuerpo bactericida sérico ("SBA") se ensayó dos semanas luego de la segunda dosis usando el método CFU estándar, o el método de Alamar Blue usando una cepa de serogrupo de *N. meningitidis* NZ98. La valoración SBA es un marcador indirecto aceptado por la Administración de Medicamentos y Alimentos de los Estados Unidos (FDA) y por la Agencia Europea para la Evaluación de Productos Medicinales (EMEA), para la eficacia de vacunas de *N. meningitidis* en humanos. Los resultados se muestran en la Figura 1 (donde la dosis del compuesto se indica en µg a la izquierda). Los cambios sobre la respuesta producidos con MF59/3MenB se muestran a la derecha de cada barra en la Figura 1.

En un segundo experimento, se evaluaron la dosis y respuesta de un compuesto, Ejemplo Nro. 47, usando el mismo protocolo. La Figura 2 muestra el resultado promedio de tres estudios de SBA independientes con desviación típica, expuesta como barras de error. Las valoraciones de SBA se midieron en todos los

casos usando el método CFU estándar. La dosis de cada compuesto en μg se indica a la izquierda de la Figura 2.

La Figura 3 muestra las valoraciones de SBA de dos estudios independientes que comparan la dosis y respuesta del Ejemplo Nro. 47 con 3MenB con coadyuvante de alumbre, en lugar del coadyuvante MF59.

La Figura 4 muestra las valoraciones de SBA de otro estudio que compra la dosis y respuesta de otro compuesto, el Ejemplo Nro.169.

La Figura 5 resume la información de los seis experimentos en total. Una valoración de > 1000 se correlaciona con la inmunización que proporciona protección contra el patógeno evaluado en la valoración de SBA (es decir, la cepa de serogrupo B de *N. meningitidis* NZ/98). En consecuencia, con una concentración de 100 μg, cada uno del Ejemplo Nro. 47, Ejemplo Nro. 169 y Ejemplo Nro. 49 pudo proporcionar una respuesta protectora en los ratones, para demostrar, por lo tanto, la capacidad de los compuestos revelados en esta solicitud para mejorar la respuesta inmunitaria a un antígeno. Solo uno de seis experimentos que utilizaron 3MenB/MF59 produjo una respuesta protectora contra la bacteria NZ98. En comparación, siete de ocho experimentos que utilizaron los compuestos revelados en esta solicitud produjeron una respuesta protectora contra la bacteria NZ98. ** y * sobre el compuesto en la Figura 5 indican una diferencia estadísticamente significativa por valor p entre la inmunización con el compuesto y la inmunización sin el compuesto (es decir, en comparación con el control 3MenB/MF59). ns indica que la diferencia no fue estadísticamente significativa por valor p. La inmunización con un oligo CpG en comparación con el Ejemplo Nro. 47 no produjo una diferencia estadísticamente significativa por valor p.

Se midió el peso corporal de los ratones en puntos de tiempo tempranos (día 1 y día 2) y tardíos (día 14 y día 28) luego de la inmunización. La

inmunización con 3MenB/MF59 en comparación con 3MenB/MF59 + Ejemplo Nro. 169 no produjo una diferencia estadísticamente significativa en el descenso de peso. Los ratones inmunizados con un oligo CpG, o con 3MenB/OMV, sí mostraron un leve aunque estadísticamente significativo descenso de peso el día 1 luego de la inmunización.

Ensayos.

Los compuestos de la Fórmula (I) proporcionados en esta solicitud se ensayaron a fin de medir su capacidad para modular receptores de tipo toll.

Ensayo de células mononucleares de sangre periférica humana.

Se ensayó la bioactividad de los compuestos descriptos en el ensayo de sangre periférica humana (PBMC humanas) usando un grupo de donantes humanos normales independientes de acuerdo con pautas aprobadas por el comité de reseña institucional. Las PBMC humanas se aislaron de sangre periférica fresca usando un gradiente de densidad Ficoll (GE healthcare 17–1440–03). Se dispusieron 30–35 ml de sangre humana periférica sobre 15 ml de Ficoll en tubos cónicos de 50 ml, y a continuación, se centrifugaron a 1800 r. p. m. (centrífuga Eppendorf Centrifuge 5810R con tapas Biohazard sobre los recipientes de tubo) a temperatura ambiente durante 30 minutos, sin aceleración ni frenado. Las capas pulidas entonces se recogieron y se transfirieron a tubos cónicos nuevos de 50 ml, y se lavaron dos veces con medio completo que consistió en RPMI 1640 (11875085 de Invitrogen Corporation, Carlsbad, California) suplementado con 10% de suero bovino fetal inactivado por calor (Gibco 10099–141), 1% de pen–estrep (Gibco # 15140–122), aminoácidos no esenciales, 1 mM (Gibco # 11140–050), piruvato sódico, 1 mM (Gibco # 11360–070), L–glutamina, 2 mM (Gibco # 25030–081) y HEPES, 1 mM (Gibco # 15630–080). Luego se contaron las células viables usando tinción de azul de tripano, se plaquearon en placas de base plana de 96 receptáculos (Becton Dickinson #

353070) a razón de 2 x 10^5 células por receptáculo en 200 µl de volumen total de medio completo. A continuación, se agregaron los compuestos en un formato de dosis y respuesta de 10 puntos, iniciando con 100 µM, dilución triple. Los receptáculos de control negativo recibieron una concentración equivalente de DMSO. Se recogieron los sobrenadantes de cultivo luego de 18–24 horas de incubación a 37°C, 5% de CO_2, y se almacenaron a –20°C hasta el uso posterior.

Se midieron las concentraciones de IL–6 en los sobrenadantes de cultivo, usando un equipo Luminex (Biorad). El análisis de la información se realizó empleando un programa informático Prism de GraphPad (San Diego, CA). Se generaron las curvas de dosis y respuesta para cada compuesto, y se determinaron los valores EC50 como la concentración que proporcionó 50% de la señal máxima.

Ensayo de genes reporteros.

Se transfectaron de manera estable células de riñón embrionario humano 293 (HEK 293) con TLR7 o TLR8 humano y un vector reportero de luciferasa conducido por NF–kB (pNifty–Luciferase). Como un ensayo de control, se usaron células Hek293 normales transfectadas con pNifty–Luc. Las células se cultivaron en DMEM suplementado con L–glutamina, 2 mM, 10% de FBS inactivado por calor, 1% de penicilina y estreptomicina, 2 µg/ml de puromicina (InvivoGen #ant–pr–5) y 5 µg/ml de blasticidina (Invitrogen #46–1120). El regulador de ensayo de luciferasa Bright–Glo™ Luciferase y el sustrato fueron suministrados por Promega, # E263B y # E264B (sustrato de ensayo y regulador, respectivamente). Las placas de base transparente de 384 receptáculos fueron suministradas por Greiner bio–one (# 789163–G), y fueron placas con código de barras de rutina GNF.

Las células se plaquearon a razón de 25.000 células por receptáculo en placas de 384 receptáculos, en un volumen final de 50 µl de medio. Se permitió

que las células se adhirieran a las placas durante el cultivo de la noche (18 horas), a 37°C y 5% de CO_2. A continuación, se suministraron a cada receptáculo los compuestos de control positivo y experimentales diluidos en forma sucesiva, y se incubaron durante 7 horas a 37°C y 5% de CO_2. Las células estimuladas solo con DMSO sirvieron también como controles negativos. Luego de la incubación, se agregaron a cada receptáculo 30 µl del regulador de ensayo de premezcla y el regulador de sustrato, de acuerdo con las instrucciones del fabricante. La señal de luminiscencia se leyó en una máquina CLIPR con un tiempo de integración de 20 segundos por placa.

Se generaron las curvas de dosis y respuesta para cada compuesto, y se determinaron los valores EC50 como la concentración que proporcionó 50% de la señal máxima.

Resultados de ciertos ensayos.

Diversos compuestos de las Fórmulas (I)–(XVI) en forma libre o en forma de sal aceptable para uso farmacéutico exhiben propiedades farmacológicas, por ejemplo, como se indica en los ensayos *in vitro* descriptos en esta solicitud. El valor EC_{50} en dichos experimentos se proporciona como aquella concentración del compuesto de ensayo en cuestión que provoca una respuesta intermedia entre el valor inicial y las respuestas máximas. En ciertos ejemplos, los compuestos de las Fórmulas (I)–(XVI) tienen valores EC_{50} de 1 nM a 200 µM. En algunos ejemplos, los compuestos de las Fórmulas (I)–(XVI) tienen valores EC_{50} de 0,01 µM a 100 µM. En otros ejemplos, los compuestos de las Fórmulas (I)–(XVI) tienen valores EC_{50} de 0,01 µM a 50 µM. En otros ejemplos, los compuestos de las Fórmulas (I)–(XVI) tienen valores EC_{50} de 0,01 µM a 25 µM. En otros ejemplos, los compuestos de las Fórmulas (I)–(XVI) tienen valores EC_{50} de 0,01 µM a 20 µM. En otros ejemplos, los compuestos de las Fórmulas (I)–(XVI) tienen valores EC_{50} de 0,01 µM a 15 µM. En otros ejemplos, los compuestos de las

Formulas (I)–(XVI) tienen valores EC_{50} de 0,01 μM a 10 μM. En otros ejemplos, los compuestos de las Fórmulas (I)–(XVI) tienen valores EC_{50} de 0,01 μM a 5 μM. En otros ejemplos, los compuestos de las Fórmulas (I)–(XVI) tienen valores EC_{50} de 0,01 μM a 2 μM. En otros ejemplos, los compuestos de las Fórmulas (I)–(XVI) tienen valores EC_{50} de 0,01 μM a 1 μM. En ciertos ejemplos, dichos valores EC_{50} se obtienen en relación con la actividad de resiquimod establecida al 100%.

En otros ejemplos, los siguientes compuestos de las Fórmulas (I)–(XVI) tienen valores EC_{50} de 1 nM a 200 μM: 2–metilbenzo[f][1,7]naftiridin–5–amina; 2–propilbenzo[f][1,7]naftiridin–5–amina; 2–etilbenzo[f][1,7]naftiridin–5–amina; 2–(3–metoxifenetil)benzo[f][1,7]naftiridin–5–amina; 8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–fenetilbenzo[f][1,7]naftiridin–5–amina; metil 5–aminobenzo[f][1,7]naftiridina–3–carboxilato; (5–aminobenzo[f][1,7]naftiridin–3–il)metanol; benzo[f][1,7]naftiridin–5–amina; (5–aminobenzo[f][1,7]naftiridin–8–il)metanol; 2–(2–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(3–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 8–clorobenzo[f][1,7]naftiridin–5–amina; etil 5–aminobenzo[f][1,7]naftiridina–9–carboxilato; 8–metoxibenzo[f][1,7]naftiridin–5–amina; 8–(trifluormetil)benzo[f][1,7]naftiridin–5–amina; 8–fluorbenzo[f][1,7]naftiridin–5–amina; 3–metilbenzo[f][1,7]naftiridin–5–amina; 3–fluorbenzo[f][1,7]naftiridin–5–amina; 2–fenetilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2–(naftalen–1–il)etil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2–(naftalen–2–il)etil)benzo[f][1,7]naftiridin–5–amina; ácido 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoico; ácido 3–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoico; 2–(3–clorofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–clorofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; (3–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)metanol; 2–(4–clorofenetil)–8–

metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–butilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–butilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–propilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(trifluormetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,5–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–propilfenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2,4,5–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,5–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–isopropilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–heptilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–isobutoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–((2–metoxietoxi)metoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(2–fenoxietoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(4–fenilbutoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(aliloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(3–fenilpropoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(heptan–4–iloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(4–metilpent–3–eniloxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–ciclohexiletoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–isopropoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(3,3–dimetilbutoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)–2–(4–(dimetilamino)fenetil)benzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)–2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; N–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)acetamida; N–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)fenil)acetamida; N–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)–4–metilbencenosulfonamida; 3–metil–9–p–tolil–9,10–dihidrobenzo[f]furo[2,3–b][1,7]naftiridin–6–amina; 4–(2–(5–amino–8–

metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzonitrilo; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–aminoetil)–3–metilbenzamida; 8–metil–2–(2–metil–4–(1H–tetrazol–5–il)fenetil)benzo[f][1,7]naftiridin–5–amina; metil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)–4–metilpentanoato; metil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)acetato; ácido 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)–4–metilpentanoico; ácido 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)acético; 6–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)hexan–1–ol; ácido 7–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)heptanoico; 11–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)undecan–1–ol; etil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)acetato; ácido 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)acético; ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propanoico; ácido 6–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)hexanoico; 8–metil–2–(2–metil–4–(metiltio)fenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(metilsulfonil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(hexiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–fenetoxifenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(pentiloxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(4–metilpentiloxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2–fluorfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(3–fluorfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–fluorfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2–(tiofen–3–il)etil)benzo[f][1,7]naftiridin–5–amina; (5–aminobenzo[f][1,7]naftiridin–2–il)metanol; 2–(3,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(3,4–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(3,5–dimetilfenetil)–8–

metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(benzofuran–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2–nitroetil)benzo[f][1,7]naftiridin–5–amina; 2–(aminometil)–8–metilbenzo[f][1,7]naftiridin–5–amina; N^2,8–dimetilbenzo[f][1,7]naftiridina–2,5–diamina; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–feniletanol; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–(4–metoxifenil)etanol; 2–(bifenil–2–il)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(2,6–dimetilpiridin–3–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(5–metoxipiridin–2–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propanoico; 5–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–4–metilpiridin–2(1H)–ona; 6–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)piridin–3–ol; 8–metil–2–(4–(trifluormetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2–(2,3–dihidro–1H–inden–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(2,3–dihidro–1H–inden–5–il)etil)benzo[f][1,7]naftiridin–5–amina; ácido (E)–3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)acrílico; (E)–etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)acrilato; (E)–8–(2–ciclopropilvinil)–2–fenetilbenzo[f][1,7]naftiridin–5–amina; 8–pentilbenzo[f][1,7]naftiridin–5–amina; (E)–8–(2–ciclopropilvinil)benzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)–2–fenetilbenzo[f][1,7]naftiridin–5–amina; (5–amino–2–fenetilbenzo[f][1,7]naftiridin–8–il)metanol; (5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)metanol; 3–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)fenol; 2–(2–metoxifenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–etilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–etilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(dimetilamino)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(piperidin–1–

il)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–ter–butilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(piperidin–1–il)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–metoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(3,5–dimetoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(2–(trifluormetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–hidroxibencimidamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzonitrilo; 8–metil–2–(4–(1–morfolinoetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–aminofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)guanidina; 8–metil–2–(4–(1–(fenetilamino)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)acetonitrilo; 2–(4–(piperidin–1–ilmetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 1–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)bencil)piperidin–4–ol; 2–(4–(aminometil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–((etilamino)metil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–aminopropan–2–il)fenetil)benzo[f][1,7]naftiridin–5–amina; ácido 1–(1–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidina–3–carboxílico; 8–metil–2–(4–(1–(fenilamino)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–etil–8–metilbenzo[f][1,7]naftiridin–5–amina; (5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)metanol; 8–metil–2–propilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(1H–indol–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–etoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–fenoxifenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2,4–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–metoxi–2–metilfenetil)–8–

metilbenzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol; 2–(2–(2,3–dihidrobenzofuran–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etanol; 3–metil–9–fenil–9,10–dihidrobenzo[f]furo[2,3–b][1,7]naftiridin–6–amina; 8–metilbenzo[f][1,7]naftiridina–2,5–diamina; 1–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)propan–2–ol; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)acetonitrilo; N–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)acetamida; 2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–(2,4–dimetilfenil)etanol; 2–(2–(6–metoxi–4–metilpiridin–3–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)butan–1–ol; metil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propanoato; 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propan–1–ol; 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)–2–metilbutan–2–ol; 2–(4–(aminometil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; (E)–etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)acrilato; etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propanoato; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbencil)propano–1,3–diol; ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propanoico; 5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridina–8–carbaldehído; etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoato; 8–metil–2–(4–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propan–2–ol; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)metanol; etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato; ácido 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoico; (4–(2–(5–amino–8–

metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)metanol; 8–metil–2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol; 8–metil–2–(4–propoxifenetil)benzo[f][1,7]naftiridin–5–amina; ácido (E)–3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)acrílico; etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propanoato; ácido 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propanoico; 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propan–1–ol; 5–aminobenzo[f][1,7]naftiridin–8–ol; 5–aminobenzo[f][1,7]naftiridina–8–carbaldehído; 1–(5–aminobenzo[f][1,7]naftiridin–8–il)etanol; 1–(5–aminobenzo[f][1,7]naftiridin–8–il)etanona; 8–isopropilbenzo[f][1,7]naftiridin–5–amina; 8–vinilbenzo[f][1,7]naftiridin–5–amina; 8–etilbenzo[f][1,7]naftiridin–5–amina; 8–(metoximetil)benzo[f][1,7]naftiridin–5–amina; (5–amino–2–(4–metoxifenetil)benzo[f][1,7]naftiridin–8–il)metanol; benzo[f][1,7]naftiridina–5,8–diamina; 8–(aminometil)benzo[f][1,7]naftiridin–5–amina; 3–fluor–8–metilbenzo[f][1,7]naftiridin–5–amina; (5–amino–3–fluorbenzo[f][1,7]naftiridin–8–il)metanol; 3–clorobenzo[f][1,7]naftiridina–5,8–diamina; 3–fluorbenzo[f][1,7]naftiridina–5,8–diamina; 8–isobutilbenzo[f][1,7]naftiridin–5–amina; (E)–8–(prop–1–enil)benzo[f][1,7]naftiridin–5–amina; 8–propilbenzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)benzo[f][1,7]naftiridin–5–amina; 8–fenetilbenzo[f][1,7]naftiridin–5–amina; (5–amino–2–(4–bromofenetil)benzo[f][1,7]naftiridin–8–il)metanol; 2–(4–metoxi–2–metilfenetil)–8–pentilbenzo[f][1,7]naftiridin–5–amina; 8–(2–ciclopropiletil)–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–5–amina; (5–amino–2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–8–il)metanol; (5–amino–2–(4–propoxifenetil)benzo[f][1,7]naftiridin–8–il)metanol; (2–(2–(1H–indol–5–il)etil)–5–aminobenzo[f][1,7]naftiridin–8–il)metanol; metil 4–(2–(5–amino–8–

metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N,3–dimetilbenzamida; N–(2–acetamidoetil)–4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N,3–dimetilbenzamida; 2–(4–metoxifenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N,N,3–trimetilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–hidroxietil)–3–metilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–3–metilbenzamida; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(pirrolidin–1–il)metanona; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dietilamino)etil)–3–metilbenzamida; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(4–etilpiperazin–1–il)metanona; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(piperazin–1–il)metanona; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metil–N–(2–(pirrolidin–1–il)etil)benzamida; 4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N,3–dimetilbenzamida; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N–metilbenzamida; 2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol; 2–(4–butoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(2–(bifenil–4–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–((1,3–dihidroisobenzofuran–1–il)metil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(2–metilaliloxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(isopentiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil propil carbonato; etil 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)pentanoato; 2–(4–

(ciclopentiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(ciclobutilmetoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 8–metil–2–(4–(2–morfolinoetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)–1–feniletanona; ácido 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)pentanoico; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)etanol; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)–N,N–dimetilacetamida; 8–metil–2–(2–metil–4–(2–morfolinoetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etanol; dietil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propilfosfonato; ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propilfosfónico; 2–(4–butoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol; 2–(2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etanol; etil 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)pentanoato; ácido 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)pentanoico; 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil etil carbonato; metil 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)butanoato; ácido 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)butanoico; ácido 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)butanoico; 2–(4–(isopentiloxi)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil hexil carbonato; 2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina; (5–amino–2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–8–il)metanol; dietil 3–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)propilfosfonato; dietil 3–

(2–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etoxi)propilfosfonato; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil dimetilsulfamato; (5–amino–2–(4–(dimetilamino)fenetil)benzo[f][1,7]naftiridin–8–il)metanol; 2–(4–(dimetilamino)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol; 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona; 2–(4–((dimetilamino)metil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(4–(1–(dimetilamino)etil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona oxima; 8–metil–2–(4–((metilamino)metil)fenetil)benzo[f][1,7]naftiridin–5–amina; (4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)bencilamino)etanol; 8–metil–2–(4–(pirrolidin–1–ilmetil)fenetil)benzo[f][1,7]naftiridin–5–amina; 2–(3,4–dimetoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; 2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)etanol; 1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanol; 8–metil–2–(4–(oxazol–5–il)fenetil)benzo[f][1,7]naftiridin–5–amina; 3–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propanonitrilo; (2R)–2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propan–1–ol; 8–metil–2–(4–(1–(piperazin–1–il)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; ((2S)–1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidin–2–il)metanol; N^1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^2,N^2–dimetiletano–1,2–diamina; ácido 3–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propanoico; 8–metil–2–(4–(1–(4–metilpiperazin–1–il)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; N^2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^1,N^1–dimetilpropano–1,2–diamina; 8–metil–2–(4–(1–(2–(piridin–4–

il)etilamino)etil)fenetil)benzo[f][1,7]naftiridin–5–amina; N^1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^2,N^2–dietiletano–1,2–diamina; 2–(4–(dimetilamino)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina; ácido 1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidina–3–carboxílico; 4–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)fenol; 1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2 il)etil)fenil)etil)pirrolidin–3–ol; y 2–(4–(2–aminopropan–2–il)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

Solo a modo de ejemplo, el compuesto benzo[f][1,7]naftiridin–5–amina (ejemplo 1) tiene un valor EC_{50} de >100 µM , 14 µM y 0,84 µM en ensayos de HEK293–TLR7, HEK293–TLR8 e IL–6 hPBMC, respectivamente.

Solo a modo de ejemplo, el compuesto 8–metilbenzo[f][1,7]naftiridin–5–amina (ejemplo 5) tiene un valor EC_{50} de 15,8 µM, 9,01 µM y 0,396 µM en ensayos de HEK293–TLR7, HEK293–TLR8 e IL–6 hPBMC, respectivamente.

Solo a modo de ejemplo, el compuesto 8–fluorbenzo[f][1,7]naftiridin–5–amina (ejemplo 14) tiene un valor EC_{50} de 37 µM y 6,38 µM en ensayos de HEK293–TLR8 e IL–6 hPBMC, respectivamente.

Solo a modo de ejemplo, el compuesto 5–aminobenzo[f][1,7]naftiridin–3(4H)–ona (ejemplo 15) tiene un valor EC_{50} de 24,1 µM en un ensayo de HEK293–TLR7.

Solo a modo de ejemplo, el compuesto 2–etilbenzo[f][1,7]naftiridin–5–amina (ejemplo 30) tiene un valor EC_{50} de 8,64 µM, 13 µM y 2,28 µM en ensayos de HEK293–TLR7, HEK293–TLR8 e IL–6 hPBMC, respectivamente.

Solo a modo de ejemplo, el compuesto 2–fenetilbenzo[f][1,7]naftiridin–5–amina (ejemplo 33) tiene un valor EC_{50} de 2,44 µM y 2,28 µM en ensayos de HEK293–TLR7 e IL–6 hPBMC.

Solo a modo de ejemplo, el valor EC_{50} para la estimulación de TLR–7 por

ciertos compuestos adicionales de la Fórmula (I) se cita en la Tabla 2 a continuación. El número de identificación de cada compuesto es el número del Ejemplo anterior que describe su síntesis.

Tabla 2

Ejemplo Nro.	**TLR–7 humano EC_{50} (nM)**
44	107
46	347
47	361
61	582
62	35
63	24
126	275
138	213
147	14
178	562

Solo a modo de ejemplo, el valor EC_{50} para la estimulación de TLR–8 por ciertos compuestos adicionales de la Fórmula (I) se cita en la Tabla 3 a continuación. El número de identificación de cada compuesto es el número del Ejemplo anterior que describe su síntesis.

Tabla 3

Ejemplo Nro.	**TLR–8 humano EC_{50} (μM)**
177	15
186	11
187	82
188	>100
189	6,2
190	4,3
191	6
193	24
195	5,3
196	2,6

Se entiende que los ejemplos y las realizaciones que se describen en la presente solicitud se presentan sólo con propósitos ilustrativos, y que los expertos en el arte podrán idear diversas modificaciones o cambios en vista de dichos ejemplos y realizaciones, que deben incluirse dentro del espíritu y alcance de esta solicitud y del alcance de las reivindicaciones adjuntas. Todas las publicaciones, patentes y solicitudes de patente citadas en esta solicitud se incorporan en la presente solicitud a modo de referencia para todos los propósitos.

LISTADO DE SECUENCIAS

<110> IRM LLC
Cortez, Alex

<120> COMPUESTOS Y COMPOSICIONES COMO MODULADORES DE LA ACTIVIDAD DE TLR

<130> P1326PC20

<160> 6

<170> PatentIn version 3.5

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20 25 30

Val Arg Lys Asn Glu Lys Leu Lys Leu Ala Ala Gln Gly Ala Glu Lys
35 40 45

Thr Tyr Gly Asn Gly Asp Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp
50 55 60

Lys Val Ser Arg Phe Asp Phe Ile Arg Gln Ile Glu Val Asp Gly Gln
65 70 75 80

Leu Ile Thr Leu Glu Ser Gly Glu Phe Gln Val Tyr Lys Gln Ser His
85 90 95

Ser Ala Leu Thr Ala Phe Gln Thr Glu Gln Ile Gln Asp Ser Glu His
100 105 110

Ser Gly Lys Met Val Ala Lys Arg Gln Phe Arg Ile Gly Asp Ile Ala
115 120 125

Gly Glu His Thr Ser Phe Asp Lys Leu Pro Glu Gly Gly Arg Ala Thr
130 135 140

Tyr Arg Gly Thr Ala Phe Gly Ser Asp Asp Ala Gly Gly Lys Leu Thr
145 150 155 160

Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly Asn Gly Lys Ile Glu His
165 170 175

Leu Lys Ser Pro Glu Leu Asn Val Asp Leu Ala Ala Ala Asp Ile Lys
180 185 190

Pro Asp Gly Lys Arg His Ala Val Ile Ser Gly Ser Val Leu Tyr Asn
195 200 205

Gln Ala Glu Lys Gly Ser Tyr Ser Leu Gly Ile Phe Gly Gly Lys Ala
210 215 220

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His Ile Gly Leu Ala Ala Lys Gln
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20 25 30

Val Arg Lys Asn Glu Lys Leu Lys Leu Ala Ala Gln Gly Ala Glu Lys
35 40 45

Thr Tyr Gly Asn Gly Asp Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp
50 55 60

Lys Val Ser Arg Phe Asp Phe Ile Arg Gln Ile Glu Val Asp Gly Gln
65 70 75 80

Leu Ile Thr Leu Glu Ser Gly Glu Phe Gln Ile Tyr Lys Gln Asp His
85 90 95

Ser Ala Val Val Ala Leu Gln Ile Glu Lys Ile Asn Asn Pro Asp Lys
100 105 110

Ile Asp Ser Leu Ile Asn Gln Arg Ser Phe Leu Val Ser Gly Leu Gly
115 120 125

Gly Glu His Thr Ala Phe Asn Gln Leu Pro Asp Gly Lys Ala Glu Tyr
130 135 140

His Gly Lys Ala Phe Ser Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr
145 150 155 160

Thr Ile Asp Phe Ala Ala Lys Gln Gly His Gly Lys Ile Glu His Leu
165 170 175

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Lys Thr Pro Glu Gln Asn Val Glu Leu Ala Ala Ala Glu Leu Lys Ala
            180                 185                 190

Asp Glu Lys Ser His Ala Val Ile Leu Gly Asp Thr Arg Tyr Gly Ser
        195                 200                 205

Glu Glu Lys Gly Thr Tyr His Leu Ala Leu Phe Gly Asp Arg Ala Gln
    210                 215                 220

Glu Ile Ala Gly Ser Ala Thr Val Lys Ile Gly Glu Lys Val His Glu
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Ile Gly Ile Ala Gly Lys Gln
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Leu Asp His Lys Asp Lys Gly Leu Lys Ser Leu Thr Leu Glu Asp Ser
            20                  25                  30

Ile Pro Gln Asn Gly Thr Leu Thr Leu Ser Ala Gln Gly Ala Glu Lys
        35                  40                  45

Thr Phe Lys Ala Gly Asp Lys Asp Asn Ser Leu Asn Thr Gly Lys Leu
    50                  55                  60

Lys Asn Asp Lys Ile Ser Arg Phe Asp Phe Val Gln Lys Ile Glu Val
65                  70                  75                  80

Asp Gly Gln Thr Ile Thr Leu Ala Ser Gly Glu Phe Gln Ile Tyr Lys
                85                  90                  95

Gln Asn His Ser Ala Val Val Ala Leu Gln Ile Glu Lys Ile Asn Asn
            100                 105                 110

Pro Asp Lys Thr Asp Ser Leu Ile Asn Gln Arg Ser Phe Leu Val Ser
        115                 120                 125

Gly Leu Gly Gly Glu His Thr Ala Phe Asn Gln Leu Pro Gly Gly Lys
    130                 135                 140

Ala Glu Tyr His Gly Lys Ala Phe Ser Ser Asp Asp Pro Asn Gly Arg
145                 150                 155                 160
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Leu His Tyr Ser Ile Asp Phe Thr Lys Lys Gln Gly Tyr Gly Arg Ile
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Glu His Leu Lys Thr Leu Glu Gln Asn Val Glu Leu Ala Ala Ala Glu
180 185 190

Leu Lys Ala Asp Glu Lys Ser His Ala Val Ile Leu Gly Asp Thr Arg
195 200 205

Tyr Gly Ser Glu Glu Lys Gly Thr Tyr His Leu Ala Leu Phe Gly Asp
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Arg Ala Gln Glu Ile Ala Gly Ser Ala Thr Val Lys Ile Gly Glu Lys
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Val His Glu Ile Gly Ile Ala Gly Lys Gln
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35 40 45

Asp Met Ala Ala Val Ser Glu Glu Asn Thr Gly Asn Gly Gly Ala Ala
50 55 60

Ala Thr Asp Lys Pro Lys Asn Glu Asp Glu Gly Ala Gln Asn Asp Met
65 70 75 80

Pro Gln Asn Ala Ala Asp Thr Asp Ser Leu Thr Pro Asn His Thr Pro
85 90 95

Ala Ser Asn Met Pro Ala Gly Asn Met Glu Asn Gln Ala Pro Asp Ala
100 105 110

Gly Glu Ser Glu Gln Pro Ala Asn Gln Pro Asp Met Ala Asn Thr Ala
115 120 125

Asp Gly Met Gln Gly Asp Asp Pro Ser Ala Gly Gly Glu Asn Ala Gly
130 135 140

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Asn Thr Ala Ala Gln Gly Thr Asn Gln Ala Glu Asn Asn Gln Thr Ala
145                 150                 155                 160

Gly Ser Gln Asn Pro Ala Ser Ser Thr Asn Pro Ser Ala Thr Asn Ser
                165                 170                 175

Gly Gly Asp Phe Gly Arg Thr Asn Val Gly Asn Ser Val Val Ile Asp
            180                 185                 190

Gly Pro Ser Gln Asn Ile Thr Leu Thr His Cys Lys Gly Asp Ser Cys
        195                 200                 205

Ser Gly Asn Asn Phe Leu Asp Glu Glu Val Gln Leu Lys Ser Glu Phe
    210                 215                 220

Glu Lys Leu Ser Asp Ala Asp Lys Ile Ser Asn Tyr Lys Lys Asp Gly
225                 230                 235                 240

Lys Asn Asp Gly Lys Asn Asp Lys Phe Val Gly Leu Val Ala Asp Ser
                245                 250                 255

Val Gln Met Lys Gly Ile Asn Gln Tyr Ile Ile Phe Tyr Lys Pro Lys
            260                 265                 270

Pro Thr Ser Phe Ala Arg Phe Arg Arg Ser Ala Arg Ser Arg Arg Ser
        275                 280                 285

Leu Pro Ala Glu Met Pro Leu Ile Pro Val Asn Gln Ala Asp Thr Leu
    290                 295                 300

Ile Val Asp Gly Glu Ala Val Ser Leu Thr Gly His Ser Gly Asn Ile
305                 310                 315                 320

Phe Ala Pro Glu Gly Asn Tyr Arg Tyr Leu Thr Tyr Gly Ala Glu Lys
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Leu Pro Gly Gly Ser Tyr Ala Leu Arg Val Gln Gly Glu Pro Ser Lys
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Gly Glu Met Leu Ala Gly Thr Ala Val Tyr Asn Gly Glu Val Leu His
        355                 360                 365

Phe His Thr Glu Asn Gly Arg Pro Ser Pro Ser Arg Gly Arg Phe Ala
    370                 375                 380

Ala Lys Val Asp Phe Gly Ser Lys Ser Val Asp Gly Ile Ile Asp Ser
385                 390                 395                 400

Gly Asp Gly Leu His Met Gly Thr Gln Lys Phe Lys Ala Ala Ile Asp
                405                 410                 415
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Gly Asn Gly Phe Lys Gly Thr Trp Thr Glu Asn Gly Gly Gly Asp Val
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Ser Gly Lys Phe Tyr Gly Pro Ala Gly Glu Glu Val Ala Gly Lys Tyr
435 440 445

Ser Tyr Arg Pro Thr Asp Ala Glu Lys Gly Gly Phe Gly Val Phe Ala
450 455 460

Gly Lys Lys Glu Gln Asp Gly Ser Gly Gly Gly Gly Ala Thr Tyr Lys
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Val Asp Glu Tyr His Ala Asn Ala Arg Phe Ala Ile Asp His Phe Asn
485 490 495

Thr Ser Thr Asn Val Gly Gly Phe Tyr Gly Leu Thr Gly Ser Val Glu
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Phe Asp Gln Ala Lys Arg Asp Gly Lys Ile Asp Ile Thr Ile Pro Val
515 520 525

Ala Asn Leu Gln Ser Gly Ser Gln His Phe Thr Asp His Leu Lys Ser
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Ala Asp Ile Phe Asp Ala Ala Gln Tyr Pro Asp Ile Arg Phe Val Ser
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Thr Lys Phe Asn Phe Asn Gly Lys Lys Leu Val Ser Val Asp Gly Asn
565 570 575

Leu Thr Met His Gly Lys Thr Ala Pro Val Lys Leu Lys Ala Glu Lys
580 585 590

Phe Asn Cys Tyr Gln Ser Pro Met Ala Lys Thr Glu Val Cys Gly Gly
595 600 605

Asp Phe Ser Thr Thr Ile Asp Arg Thr Lys Trp Gly Val Asp Tyr Leu
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        35                  40                  45

Thr Lys Gly Tyr Thr Pro Gln Ile Ser Val Val Gly Tyr Asn Arg His
    50                  55                  60

Leu Leu Leu Leu Gly Gln Val Ala Thr Glu Gly Glu Lys Gln Phe Val
65                  70                  75                  80

Gly Gln Ile Ala Arg Ser Glu Gln Ala Ala Glu Gly Val Tyr Asn Tyr
                85                  90                  95

Ile Thr Val Ala Ser Leu Pro Arg Thr Ala Gly Asp Ile Ala Gly Asp
            100                 105                 110

Thr Trp Asn Thr Ser Lys Val Arg Ala Thr Leu Leu Gly Ile Ser Pro
        115                 120                 125

Ala Thr Gln Ala Arg Val Lys Ile Val Thr Tyr Gly Asn Val Thr Tyr
    130                 135                 140

Val Met Gly Ile Leu Thr Pro Glu Glu Gln Ala Gln Ile Thr Gln Lys
145                 150                 155                 160

Val Ser Thr Thr Val Gly Val Gln Lys Val Ile Thr Leu Tyr Gln Asn
                165                 170                 175

Tyr Val Gln Arg Gly Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly
            180                 185                 190

Ala Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys
        195                 200                 205

Gly Leu Gln Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys
    210                 215                 220

Leu Lys Leu Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp
225                 230                 235                 240

Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp
                245                 250                 255

Phe Ile Arg Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser
            260                 265                 270
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Gly Glu Phe Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Phe
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Gln Thr Glu Gln Ile Gln Asp Ser Glu His Ser Gly Lys Met Val Ala
290 295 300

Lys Arg Gln Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe
305 310 315 320

Asp Lys Leu Pro Glu Gly Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe
325 330 335

Gly Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala
340 345 350

Ala Lys Gln Gly Asn Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu
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Ala Val Ile Ser Gly Ser Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser
385 390 395 400

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Lys Gln

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Thr Ile Tyr Asp Ile Asp Glu Asp Gly Thr Ile Thr Lys Lys Asp Ala
35 40 45

Thr Ala Ala Asp Val Glu Ala Asp Asp Phe Lys Gly Leu Gly Leu Lys
50 55 60

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Lys Val Val Thr Asn Leu Thr Lys Thr Val Asn Glu Asn Lys Gln Asn
65                  70                  75                  80

Val Asp Ala Lys Val Lys Ala Ala Glu Ser Glu Ile Glu Lys Leu Thr
                85                  90                  95

Thr Lys Leu Ala Asp Thr Asp Ala Ala Leu Ala Asp Thr Asp Ala Ala
            100                 105                 110

Leu Asp Ala Thr Thr Asn Ala Leu Asn Lys Leu Gly Glu Asn Ile Thr
        115                 120                 125

Thr Phe Ala Glu Glu Thr Lys Thr Asn Ile Val Lys Ile Asp Glu Lys
    130                 135                 140

Leu Glu Ala Val Ala Asp Thr Val Asp Lys His Ala Glu Ala Phe Asn
145                 150                 155                 160

Asp Ile Ala Asp Ser Leu Asp Glu Thr Asn Thr Lys Ala Asp Glu Ala
                165                 170                 175

Val Lys Thr Ala Asn Glu Ala Lys Gln Thr Ala Glu Glu Thr Lys Gln
            180                 185                 190

Asn Val Asp Ala Lys Val Lys Ala Ala Glu Thr Ala Ala Gly Lys Ala
        195                 200                 205

Glu Ala Ala Ala Gly Thr Ala Asn Thr Ala Ala Asp Lys Ala Glu Ala
    210                 215                 220

Val Ala Ala Lys Val Thr Asp Ile Lys Ala Asp Ile Ala Thr Asn Lys
225                 230                 235                 240

Asp Asn Ile Ala Lys Lys Ala Asn Ser Ala Asp Val Tyr Thr Arg Glu
                245                 250                 255

Glu Ser Asp Ser Lys Phe Val Arg Ile Asp Gly Leu Asn Ala Thr Thr
            260                 265                 270

Glu Lys Leu Asp Thr Arg Leu Ala Ser Ala Glu Lys Ser Ile Ala Asp
        275                 280                 285

His Asp Thr Arg Leu Asn Gly Leu Asp Lys Thr Val Ser Asp Leu Arg
    290                 295                 300

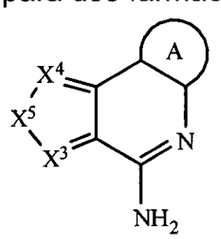
Lys Glu Thr Arg Gln Gly Leu Ala Glu Gln Ala Ala Leu Ser Gly Leu
305                 310                 315                 320

Phe Gln Pro Tyr Asn Val Gly
                325
```

REIVINDICACIONES

Habiendo así especialmente descripto y determinado la naturaleza de la presente invención y la forma como la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo:

1. Un compuesto de la Fórmula (I–A), o una sal aceptable para uso farmacéutico o un solvato aceptable para uso farmacéutico de dicho compuesto:



Fórmula (I–A)

caracterizado porque:

X^3 es N;

X^4 es N o CR^3;

X^5 es $–CR^4=CR^5–$;

R^3 es H;

R^4 y R^5 se seleccionan, de manera independiente, de H, halógeno, $–C(O)OR^7$, $–C(O)R^7$, $–C(O)N(R^{11}R^{12})$, $–N(R^{11}R^{12})$, $–N(R^9)_2$, $–NHN(R^9)_2$, $–SR^7$, $–(CH_2)_nOR^7$, $–(CH_2)_nR^7$, $–LR^8$, $–LR^{10}$, $–OLR^8$, $–OLR^{10}$, alquilo $C_1–C_6$, heteroalquilo $C_1–C_6$, haloalquilo $C_1–C_6$, alqueno $C_2–C_8$, alquino $C_2–C_8$, alcoxi $C_1–C_6$, haloalcoxi $C_1–C_6$, arilo, heteroarilo, cicloalquilo $C_3–C_8$ y heterocicloalquilo $C_3–C_8$, donde los grupos alquilo $C_1–C_6$, heteroalquilo $C_1–C_6$, haloalquilo $C_1–C_6$, alqueno $C_2–C_8$, alquino $C_2–C_8$, alcoxi $C_1–C_6$, haloalcoxi $C_1–C_6$, arilo, heteroarilo, cicloalquilo $C_3–C_8$ y heterocicloalquilo $C_3–C_8$ de R^4 y R^5, de manera independiente, están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de modo independiente de halógeno, –CN, $-NO_2$, $–R^7$, $–OR^8$, $–C(O)R^8$, $–OC(O)R^8$, $–C(O)OR^8$, $–N(R^9)_2$,

$-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-C(O)N(R^9)_2$, $-S(O)_2R^8$, $-S(O)R^8$, $-S(O)_2N(R^9)_2$ y $-NR^9S(O)_2R^8$;

o R^3 y R^4, o R^4 y R^5, cuando se presentan en átomos de anillo adyacentes, pueden estar opcionalmente ligados para formar un anillo de 5–6 miembros, donde el anillo de 5-6 miembros está opcionalmente sustituido con R^7;

cada L se selecciona de manera independiente de un enlace, $-(O(CH_2)_m)_t-$, alquilo C_1–C_6, alquenileno C_2–C_6 y alquinileno C_2–C_6, donde los grupos alquilo C_1–C_6, alquenileno C_2–C_6 y alquinileno C_2–C_6 de L están, cada uno, opcionalmente sustituidos con 1 a 4 sustituyentes seleccionados independientemente de halógeno, $-R^8$, $-OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, y $-OP(O)(OR^{10})_2$;

R^7 se selecciona de H, alquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6 y heterocicloalquilo C_3–C_8, donde los grupos alquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6 y heterocicloalquilo C_3–C_8 de R^7, de manera independiente, están opcionalmente sustituidos con 1 a 3 grupos R^{13}, y cada R^{13} se selecciona de modo independiente de halógeno, –CN, $-LR^9$, $-LOR^9$, $-OLR^9$, $-LR^{10}$, $-LOR^{10}$, $-OLR^{10}$, $-LR^8$, $-LOR^8$, $-OLR^8$, $-LSR^8$, $-LSR^{10}$, $-LC(O)R^8$, $-OLC(O)R^8$, $-LC(O)OR^8$, $-LC(O)R^{10}$, $-LOC(O)OR^8$, $-LC(O)NR^9R^{11}$, $-LC(O)NR^9R^8$, $-LN(R^9)_2$, $-LNR^9R^8$, $-LNR^9R^{10}$, $-LC(O)N(R^9)_2$, $-LS(O)_2R^8$, $-LS(O)R^8$, $-LC(O)NR^8OH$, $-LNR^9C(O)R^8$, $-LNR^9C(O)OR^8$, $-LS(O)_2N(R^9)_2$, $-OLS(O)_2N(R^9)_2$, $-LNR^9S(O)_2R^8$, $-LC(O)NR^9LN(R^9)_2$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$ y $-OLP(O)(OR^{10})_2$;

cada R^8 se selecciona de manera independiente de H, $-CH(R^{10})_2$, alquilo C_1–C_8, alqueno C_2–C_8, alquino C_2–C_8, haloalquilo C_1–C_6, alcoxi C_1–C_6,

heteroalquilo C_1–C_6, cicloalquilo C_3–C_8, heterocicloalquilo C_2–C_8, hidroxialquilo C_1–C_6, y haloalcoxi C_1–C_6, donde los grupos alquilo C_1–C_8, alqueno C_2–C_8, alquino C_2–C_8, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alcoxi C_1–C_6, cicloalquilo C_3–C_8, heterocicloalquilo C_2–C_8, hidroxialquilo C_1–C_6 y haloalcoxi C_1–C_6 de R^8 están, cada uno, opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente de –CN, R^{11}, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-OC(O)R^{11}$, $-C(O)N(R^9)_2$, $-C(O)OR^{11}$, $-NR^9C(O)R^{11}$, $-NR^9R^{10}$, $-NR^{11}R^{12}$, $-N(R^9)_2$, $-OR^9$, $-OR^{10}$, $-C(O)NR^{11}R^{12}$, $-C(O)NR^{11}OH$, $-S(O)_2R^{11}$, $-S(O)R^{11}$, $-S(O)_2NR^{11}R^{12}$, $-NR^{11}S(O)_2R^{11}$, $-P(O)(OR^{11})_2$, y $-OP(O)(OR^{11})_2$;

cada R^9 se selecciona de manera independiente de H, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-S(O)_2R^{10}$, alquilo C_1–C_6, heteroalquilo C_1–C_6 y cicloalquilo C_3–C_6; o cada R^9 es, de modo independiente, un alquilo C_1–C_6 que junto con N, se une para formar un heterocicloalquilo C_3–C_8, donde el anillo heterocicloalquilo C_3–C_8 contiene opcionalmente un heteroátomo adicional seleccionado de N, O y S, y donde los grupos alquilo C_1–C_6, heteroalquilo C_1–C_6, cicloalquilo C_3–C_6, o heterocicloalquilo C_3–C_8 de R^9 están, cada uno, opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente de –CN, R^{11}, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-OC(O)R^{11}$, $-C(O)OR^{11}$, $-NR^{11}R^{12}$, $-C(O)NR^{11}R^{12}$, $-C(O)NR^{11}OH$, $-S(O)_2R^{11}$, $-S(O)R^{11}$, $-S(O)_2NR^{11}R^{12}$, $-NR^{11}S(O)_2R^{11}$, $-P(O)(OR^{11})_2$, y $-OP(O)(OR^{11})_2$;

cada R^{10} se selecciona de manera independiente de arilo, cicloalquilo C_3–C_8, heterocicloalquilo C_3–C_8 y heteroarilo, donde los grupos arilo, cicloalquilo C_3–C_8, heterocicloalquilo C_3–C_8 y heteroarilo están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de halógeno, $-R^8$, $-OR^8$, $-LR^9$, $-LOR^9$, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9CO_2R^8$, $-CO_2R^8$, $-C(O)R^8$ y $-C(O)N(R^9)_2$;

R^{11} y R^{12} se seleccionan de manera independiente de H, alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y

heterocicloalquilo C_3–C_8, donde los grupos alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8 de R^{11} y R^{12}, de modo independiente, están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de manera independiente de halógeno, –CN, R^8, $-OR^8$, $-C(O)R^8$, $^-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-NR^8C(O)R^8$, $-NR^8C(O)OR^8$, $-C(O)N(R^9)_2$, heterocicloalquilo C_3–C_8, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$, $-NR^9S(O)_2R^8$, haloalquilo C_1–C_6 y haloalcoxi C_1–C_6;

o R^{11} y R^{12} son, de manera independiente, alquilo C_1–C_6, y tomados junto con el átomo de N al cual están unidos forman un anillo heterocicloalquilo C_3–C_8 opcionalmente sustituido, que contiene opcionalmente un heteroátomo adicional seleccionado de N, O y S;

el anillo A es un arilo o un heteroarilo, donde los grupos arilo y heteroarilo del anillo A están opcionalmente sustituidos con 1 a 3 grupos R^A, donde cada R^A se selecciona de manera independiente de $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, –CN, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$ y $-(CH_2)_nNHC(O)R^8$; o dos sustituyentes R^A adyacentes en el anillo A forman un anillo de 5–6 miembros que contiene hasta dos heteroátomos como miembros de anillo; y

n es, de manera independiente en cada aparición, 0; 1; 2; 3; 4; 5; 6; 7 u 8; cada m se selecciona de manera independiente de 1; 2; 3; 4; 5 y 6, y

t es 1; 2; 3; 4; 5; 6; 7 u 8.

2. El compuesto de la reivindicación 1, caracterizado porque:

uno de R^4 y R^5 es H;

y el otro de R^4 y R^5 se selecciona de halógeno, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, $-SR^7$, $-(CH_2)_nOR^7$, $-(CH_2)_nR^7$, alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8, donde los grupos alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8 de R^4 y R^5 están opcionalmente sustituidos de manera independiente con 1 a 3 sustituyentes seleccionados de modo independiente de halógeno, $-CN$, $-R^7$, $-OR^8$, $-C(O)R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-C(O)N(R^9)_2$, $-S(O)_2R^8$, $-S(O)_2N(R^9)_2$ y $-NR^9S(O)_2R^8$.

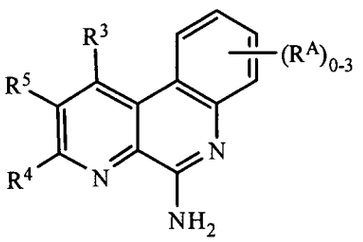
3. El compuesto de cualquiera de las reivindicaciones 1–2, caracterizado porque el anillo A es fenilo, naftilo, fluorenilo, indenilo, azulenilo o antracenilo, donde cada uno está opcionalmente sustituido con 1 a 3 grupos R^A, donde cada R^A se selecciona de manera independiente de $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, $-CN$, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)-N(R^9)_2$ y $-(CH_2)_nNHC(O)R^8$.

4. El compuesto de la reivindicación 3, caracterizado porque el anillo A es fenilo o naftilo.

5. El compuesto de cualquiera de las reivindicaciones 1–2, caracterizado porque el anillo A es benzofuranilo, benzofurazanilo, benzoxazolilo, benzopiranilo, benztiazolilo, benzotienilo, benzazepinilo, bencimidazolilo, benzotiopiranilo, benzo[1,3]dioxol, benzo[b]furilo, benzo[b]tienilo, cinolinilo, furazanilo, furilo, furopiridinilo, imidazolilo, indolilo, indolizinilo, indolin–2–ona, indazolilo, isoindolilo, isoquinolinilo, isoxazolilo, isotiazolilo, 1,8–naftiridinilo, oxazolilo, oxaindolilo, oxadiazolilo, pirazolilo, pirrolilo, ftalazinilo, pteridinilo, purinilo, piridilo, piridazinilo, pirazinilo, pirimidinilo, quinoxalinilo, quinolinilo, quinazolinilo, 4H–quinolizinilo, tiazolilo, tiadiazolilo, tienilo, triazinilo, triazolilo o tetrazolilo, cada uno de los cuales está opcionalmente sustituido con 1 a 3 grupos R^A, donde cada R^A se selecciona de manera independiente de $-R^8$, $-R^7$, $-OR^7$, $-OR^8$, $-R^{10}$, $-OR^{10}$, $-SR^8$, $-NO_2$, $-CN$, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9C(S)R^8$, $-NR^9C(O)N(R^9)_2$, $-NR^9C(S)N(R^9)_2$, $-NR^9CO_2R^8$, $-NR^9NR^9C(O)R^8$, $-NR^9NR^9C(O)N(R^9)_2$, $-NR^9NR^9CO_2R^8$, $-C(O)C(O)R^8$, $-C(O)CH_2C(O)R^8$, $-CO_2R^8$, $-(CH_2)_nCO_2R^8$, $-C(O)R^8$, $-C(S)R^8$, $-C(O)N(R^9)_2$, $-C(S)N(R^9)_2$, $-OC(O)N(R^9)_2$, $-OC(O)R^8$, $-C(O)N(OR^8)R^8$, $-C(NOR^8)R^8$, $-S(O)_2R^8$, $-S(O)_3R^8$, $-SO_2N(R^9)_2$, $-S(O)R^8$, $-NR^9SO_2N(R^9)_2$, $-NR^9SO_2R^8$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, $-OP(O)(OR^{10})_2$, $-N(OR^8)R^8$, $-CH=CHCO_2R^8$, $-C(=NH)–N(R^9)_2$ y $-(CH_2)_nNHC(O)R^8$.

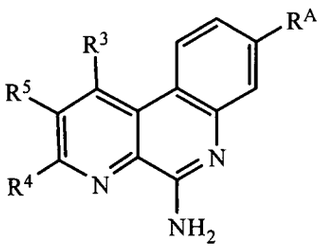
6. El compuesto de la reivindicación 5, caracterizado porque el anillo A es piridilo, benzo[1,3]dioxol, tienilo, benzotienilo, benzofuranilo o indolilo.

7. El compuesto de cualquiera de las reivindicaciones 1–3, caracterizado porque el compuesto tiene una estructura de la Fórmula (X–A):



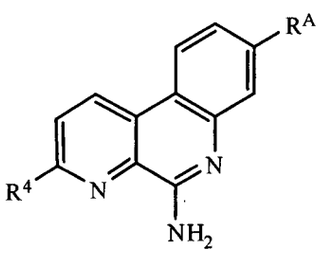
Fórmula (X–A).

8. El compuesto de la reivindicación 7, caracterizado porque el compuesto tiene una estructura de la Fórmula (XI):

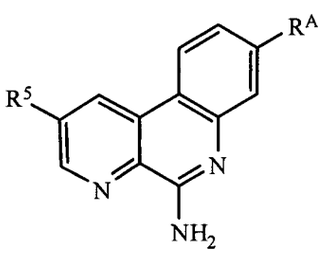


Fórmula (XI).

9. El compuesto de cualquiera de las reivindicaciones 1–8, caracterizado porque el compuesto tiene una estructura de la Fórmula (XII) o Fórmula (XIII):



Fórmula (XII)



Fórmula (XIII).

10. El compuesto de cualquiera de las reivindicaciones 1–9, caracterizado porque:

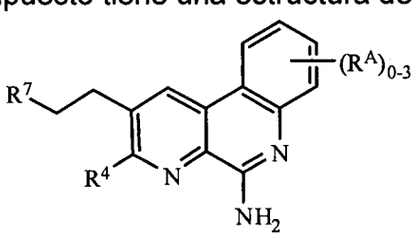
R^4 y R^5 se seleccionan de modo independiente de H, halógeno, $-C(O)OR^7$, $-C(O)R^7$, $-C(O)N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-N(R^9)_2$, $-NHN(R^9)_2$, $-LR^8$, $-LR^{10}$, $-OLR^8$, $-OLR^{10}$, $-SR^7$, $-(CH_2)_nR^7$, $-(CH_2)_nOR^7$, alquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8 y alcoxi C_1–C_6, donde los grupos alquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8 y alcoxi C_1–C_6 de R^4 y R^5, de manera

independiente, están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de modo independiente de halógeno, –CN, $–R^7$, $–OR^8$, $–C(O)R^8$, $–OC(O)R^8$, $–C(O)OR^8$, $–N(R^9)_2$, $–P(O)(OR^8)_2$, $–OP(O)(OR^8)_2$, $–P(O)(OR^{10})_2$, $–OP(O)(OR^{10})_2$, $–C(O)N(R^9)_2$, $–S(O)_2R^8$, $–S(O)_2N(R^9)_2$ y $–NHS(O)_2R^8$.

11. El compuesto de cualquiera de las reivindicaciones 1–10, caracterizado porque:

R^4 y R^5 se seleccionan de manera independiente de H, halógeno, $–C(O)OR^7$, $–C(O)R^7$, $–C(O)N(R^{11}R^{12})$, $–N(R^{11}R^{12})$, $–N(R^9)_2$, $–NHN(R^9)_2$, $–LR^8$, $–LR^{10}$, $–OLR^8$, $–OLR^{10}$, $–SR^7$, $–(CH_2)_nOR^7$, $–(CH_2)_nR^7$, alquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8 y alcoxi C_1–C_6, donde los grupos alquilo –C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8 y alcoxi C_1–C_6, de modo independiente, están opcionalmente sustituidos con R^7.

12. El compuesto de cualquiera de las reivindicaciones 1–11, caracterizado porque compuesto tiene una estructura de la Fórmula (XIV):



Fórmula (XIV).

13. El compuesto de cualquiera de las reivindicaciones 1–12, caracterizado porque:

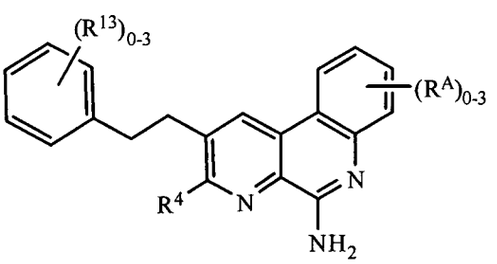
R^7 se selecciona de H, alquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8, donde los grupos alquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8 de R^7 de manera independiente están opcionalmente sustituidos con 1 a 3 grupos R^{13}, y cada R^{13} se selecciona de manera independiente de halógeno, –CN, $–LR^9$, $–LOR^9$, $–OLR^9$, $–LR^{10}$, $–LOR^{10}$, $–OLR^{10}$, $–LR^8$, $–LOR^8$, $–OLR^8$, $–LSR^8$, $–LSR^{10}$, $–LC(O)R^8$, $–OLC(O)R^8$, $–LC(O)OR^8$, $–LC(O)R^{10}$, $–LOC(O)OR^8$, $–LC(O)NR^9R^{11}$, $–LC(O)NR^9R^8$, $–LN(R^9)_2$,

$-LNR^9R^8$, $-LNR^9R^{10}$, $-LC(O)N(R^9)_2$, $-LS(O)_2R^8$, $-LS(O)R^8$, $-LC(O)NR^8OH$, $-LNR^9C(O)R^8$, $-LNR^9C(O)OR^8$, $-LS(O)_2N(R^9)_2$, $-OLS(O)_2N(R^9)_2$, $-LNR^9S(O)_2R^8$, $-LC(O)NR^9LN(R^9)_2$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$ y $-OLP(O)(OR^{10})_2$.

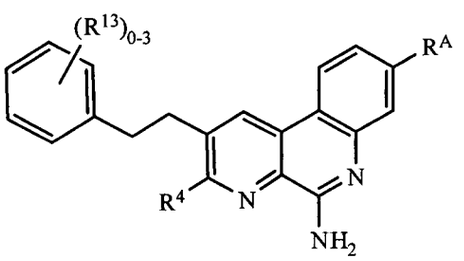
14. El compuesto de cualquiera de las reivindicaciones 1–13, caracterizado porque:

R^7 se selecciona de H, alquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8, donde los grupos alquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8 de manera independiente están opcionalmente sustituidos con 1–3 grupos R^{13}, y cada R^{13} se selecciona de modo independiente de halógeno, haloalquilo C_1–C_6, $-LR^8$, LR^9, $-LOR^8$ y $-OLR^8$.

15. El compuesto de cualquiera de las reivindicaciones 1–14, caracterizado porque el compuesto tiene una estructura de la Fórmula (XV) o la Fórmula (XVI):



Fórmula (XV)



Fórmula (XVI).

16. El compuesto de cualquiera de las reivindicaciones 1–15, caracterizado porque:

R^{13} se selecciona de $–LR^9$, $–LOR^9$, $–OLR^9$, $–LR^{10}$, $–LOR^{10}$, $–OLR^{10}$, $–LR^8$, $–LOR^8$, $–OLR^8$, $–LSR^8$, $–LSR^{10}$, $–LC(O)R^8$, $–OLC(O)R^8$, $–LC(O)OR^8$, $–LC(O)R^{10}$, $–LOC(O)OR^8$, $–LC(O)NR^9R^{11}$, $–LC(O)NR^9R^8$, $–LN(R^9)_2$, $–LNR^9R^8$, $–LNR^9R^{10}$, $–LC(O)N(R^9)_2$, $–LS(O)_2R^8$, $–LS(O)R^8$, $–LC(O)NR^8OH$, $–LNR^9C(O)R^8$, $–LNR^9C(O)OR^8$, $–LS(O)_2N(R^9)_2$, $–OLS(O)_2N(R^9)_2$, $–LNR^9S(O)_2R^8$, $–LC(O)NR^9LN(R^9)_2$, $–LP(O)(OR^8)_2$, $–LOP(O)(OR^8)_2$, $–LP(O)(OR^{10})_2$ y $–OLP(O)(OR^{10})_2$.

17. El compuesto de cualquiera de las reivindicaciones 1–16, caracterizado porque:

R^{10} es un arilo o un heteroarilo, donde los grupos arilo y heteroarilo están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de halógeno, $–R^8$, $–OR^8$, $–LR^9$, $–LOR^9$ y $–N(R^9)_2$.

18. El compuesto de cualquiera de las reivindicaciones 1–17, caracterizado porque:

R^{10} es fenilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de halógeno, $–R^8$, $–OR^8$ y $–N(R^9)_2$.

19. El compuesto de cualquiera de las reivindicaciones 1–18, caracterizado porque:

cada R^A se selecciona de manera independiente de $–R^7$, $–OR^7$, $–R^8$, $–OR^8$, $–R^{10}$, $–OR^{10}$, $–SR^8$, $–N(R^9)_2$, $–S(O)_2R^8$, $–S(O)_3R^8$, $–SO_2N(R^9)_2$, $–S(O)R^8$, $–NR^9SO_2N(R^9)_2$, $–CH=CHCO_2R^8$, $(CH_2)_nCO_2R^8$, $–NR^9SO_2R^8$, $–P(O)(OR^8)_2$, $–OP(O)(OR^8)_2$, $–P(O)(OR^{10})_2$ y $–OP(O)(OR^{10})_2$.

20. El compuesto de cualquiera de las reivindicaciones 1–19, caracterizado porque:

R^8 se selecciona de H, alquilo C_1–C_6 y haloalquilo C_1–C_6.

21. El compuesto de la reivindicación 1, seleccionado de:

2–metilbenzo[f][1,7]naftiridin–5–amina,

2–propilbenzo[f][1,7]naftiridin–5–amina,

2–etilbenzo[f][1,7]naftiridin–5–amina,

2–(3–metoxifenetil)benzo[f][1,7]naftiridin–5–amina,

8–metilbenzo[f][1,7]naftiridin–5–amina,

8–metil–2–fenetilbenzo[f][1,7]naftiridin–5–amina,

metil 5–aminobenzo[f][1,7]naftiridina–3–carboxilato,

(5–aminobenzo[f][1,7]naftiridin–3–il)metanol,

benzo[f][1,7]naftiridin–5–amina,

(5–aminobenzo[f][1,7]naftiridin–8–il)metanol,

2–(2–metilfenetil)benzo[f][1,7]naftiridin–5–amina,

2–(3–metilfenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–metilfenetil)benzo[f][1,7]naftiridin–5–amina,

8–clorobenzo[f][1,7]naftiridin–5–amina,

etil 5–aminobenzo[f][1,7]naftiridina–9–carboxilato,

8–metoxibenzo[f][1,7]naftiridin–5–amina,

8–(trifluormetil)benzo[f][1,7]naftiridin–5–amina,

8–fluorbenzo[f][1,7]naftiridin–5–amina,

3–metilbenzo[f][1,7]naftiridin–5–amina,

3–fluorbenzo[f][1,7]naftiridin–5–amina,

2–fenetilbenzo[f][1,7]naftiridin–5–amina,

8–metil–2–(2–(naftalen–1–il)etil)benzo[f][1,7]naftiridin–5–amina,

8–metil–2–(2–(naftalen–2–il)etil)benzo[f][1,7]naftiridin–5–amina,

ácido 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoico,

ácido 3–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoico,

2–(3–clorofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(2–clorofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

(3–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)metanol,

2–(4–clorofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(4–butilfenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–butilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(4–propilfenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–(trifluormetil)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(2,5–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

8–metil–2–(4–propilfenetil)benzo[f][1,7]naftiridin–5–amina,

8–metil–2–(2,4,5–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina,

2–(2,5–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–isopropilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(4–heptilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(4–isobutoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(4–((2–metoxietoxi)metoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

8–metil–2–(4–(2–fenoxietoxi)fenetil)benzo[f][1,7]naftiridin–5–amina,

8–metil–2–(4–(4–fenilbutoxi)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–(aliloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

8–metil–2–(4–(3–fenilpropoxi)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–(heptan–4–iloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

8–metil–2–(4–(4–metilpent–3–eniloxi)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–(2–ciclohexiletoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(4–isopropoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(4–(3,3–dimetilbutoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

8–(2–ciclopropiletil)–2–(4–(dimetilamino)fenetil)benzo[f][1,7]naftiridin–5–amina,

8–(2–ciclopropiletil)–2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina,

N–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)acetamida,

N–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)fenil)acetamida,

N–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)–4–metilbencenosulfonamida,

3–metil–9–p–tolil–9,10–dihidrobenzo[f]furo[2,3–b][1,7]naftiridin–6–amina,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzonitrilo,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–aminoetil)–3–metilbenzamida,

8–metil–2–(2–metil–4–(1H–tetrazol–5–il)fenetil)benzo[f][1,7]naftiridin–5–amina,

metil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)–4–metilpentanoato,

metil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)acetato,

ácido 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)–4–metilpentanoico,

ácido 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamido)acético,

6–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)hexan–1–ol,

ácido 7–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)heptanoico,

11–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)undecan–1–ol,

etil 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)acetato,

ácido 2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)acético,

ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propanoico,

ácido 6–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)hexanoico,

8–metil–2–(2–metil–4–(metiltio)fenetil)benzo[f][1,7]naftiridin–5–amina,

8–metil–2–(4–(metilsulfonil)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–(hexiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

8–metil–2–(4–fenetoxifenetil)benzo[f][1,7]naftiridin–5–amina,

8–metil–2–(4–(pentiloxi)fenetil)benzo[f][1,7]naftiridin–5–amina,

8–metil–2–(4–(4–metilpentiloxi)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(2–fluorfenetil)benzo[f][1,7]naftiridin–5–amina,

2–(3–fluorfenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–fluorfenetil)benzo[f][1,7]naftiridin–5–amina,

2–(2–(tiofen–3–il)etil)benzo[f][1,7]naftiridin–5–amina,

(5–aminobenzo[f][1,7]naftiridin–2–il)metanol,

2–(3,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina,

2–(3,4–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(3,5–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(2–(benzofuran–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

8–metil–2–(2–nitroetil)benzo[f][1,7]naftiridin–5–amina,

2–(aminometil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

N^2,8–dimetilbenzo[f][1,7]naftiridina–2,5–diamina,

2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–feniletanol,

2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–(4–metoxifenil)etanol,

2–(bifenil–2–il)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(2–(2,6–dimetilpiridin–3–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(2–(5–metoxipiridin–2–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propanoico,

5–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–4–metilpiridin–2(1H)–ona,

6–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)piridin–3–ol,

8–metil–2–(4–(trifluormetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(2–(2,3–dihidro–1H–inden–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(2–(2,3–dihidro–1H–inden–5–il)etil)benzo[f][1,7]naftiridin–5–amina,

ácido (E)–3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)acrílico,

(E)–etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)acrilato,

(E)–8–(2–ciclopropilvinil)–2–fenetilbenzo[f][1,7]naftiridin–5–amina,

8–pentilbenzo[f][1,7]naftiridin–5–amina,

(E)–8–(2–ciclopropilvinil)benzo[f][1,7]naftiridin–5–amina,

8–(2–ciclopropiletil)–2–fenetilbenzo[f][1,7]naftiridin–5–amina,

(5–amino–2–fenetilbenzo[f][1,7]naftiridin–8–il)metanol,

(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)metanol,

3–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)fenol,

2–(2–metoxifenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–etilfenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–etilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(4–(dimetilamino)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–(piperidin–1–il)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–ter–butilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

8–metil–2–(4–(piperidin–1–il)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–metoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(3,5–dimetoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

8–metil–2–(2–(trifluormetil)fenetil)benzo[f][1,7]naftiridin–5–amina,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–hidroxibencimidamida,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzonitrilo,

8–metil–2–(4–(1–morfolinoetil)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–aminofenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)guanidina,

8–metil–2–(4–(1–(fenetilamino)etil)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)acetonitrilo,

2–(4–(piperidin–1–ilmetil)fenetil)benzo[f][1,7]naftiridin–5–amina,

1–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)bencil)piperidin–4–ol,

2–(4–(aminometil)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–((etilamino)metil)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–(2–aminopropan–2–il)fenetil)benzo[f][1,7]naftiridin–5–amina,

ácido 1–(1–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidina–3–carboxílico,

8–metil–2–(4–(1–(fenilamino)etil)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–etil–8–metilbenzo[f][1,7]naftiridin–5–amina,

(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)metanol,

8–metil–2–propilbenzo[f][1,7]naftiridin–5–amina,

2–(2–(1H–indol–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(4–etoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

8–metil–2–(4–fenoxifenetil)benzo[f][1,7]naftiridin–5–amina,

2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina,

2–(2,4–dimetilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(4–metoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenol,

2–(2–(2,3–dihidrobenzofuran–5–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etanol,

3–metil–9–fenil–9,10–dihidrobenzo[f]furo[2,3–b][1,7]naftiridin–6–amina,

8–metilbenzo[f][1,7]naftiridina–2,5–diamina,

1–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)propan–2–ol,

2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)acetonitrilo,

N–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)acetamida,

2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)–1–(2,4–dimetilfenil)etanol,

2–(2–(6–metoxi–4–metilpiridin–3–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)butan–1–ol,

metil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propanoato,

3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propan–1–ol,

4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)–2–metilbutan–2–ol,

2–(4–(aminometil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

(E)–etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)acrilato,

etil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propanoato,

2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbencil)propano–1,3–diol,

ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propanoico,

5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridina–8–carbaldehído,

etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)benzoato,

8–metil–2–(4–metilfenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)propan–2–ol,

(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)metanol,

etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato,

ácido 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoico,

(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)metanol,

8–metil–2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol,

8–metil–2–(4–propoxifenetil)benzo[f][1,7]naftiridin–5–amina,

ácido (E)–3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)acrílico,

etil 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propanoato,

ácido 3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propanoico,

3–(5–amino–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–8–il)propan–1–ol,

5–aminobenzo[f][1,7]naftiridin–8–ol,

5–aminobenzo[f][1,7]naftiridina–8–carbaldehído,

1–(5–aminobenzo[f][1,7]naftiridin–8–il)etanol,

1–(5–aminobenzo[f][1,7]naftiridin–8–il)etanona,

8–isopropilbenzo[f][1,7]naftiridin–5–amina,

8–vinilbenzo[f][1,7]naftiridin–5–amina,

8–etilbenzo[f][1,7]naftiridin–5–amina,

8–(metoximetil)benzo[f][1,7]naftiridin–5–amina,

(5–amino–2–(4–metoxifenetil)benzo[f][1,7]naftiridin–8–il)metanol,

benzo[f][1,7]naftiridina–5,8–diamina,

8–(aminometil)benzo[f][1,7]naftiridin–5–amina,

3–fluor–8–metilbenzo[f][1,7]naftiridin–5–amina,

(5–amino–3–fluorbenzo[f][1,7]naftiridin–8–il)metanol,

3–clorobenzo[f][1,7]naftiridina–5,8–diamina,

3–fluorbenzo[f][1,7]naftiridina–5,8–diamina,

8–isobutilbenzo[f][1,7]naftiridin–5–amina,

(E)–8–(prop–1–enil)benzo[f][1,7]naftiridin–5–amina,

8–propilbenzo[f][1,7]naftiridin–5–amina,

8–(2–ciclopropiletil)benzo[f][1,7]naftiridin–5–amina,

8–fenetilbenzo[f][1,7]naftiridin–5–amina,

(5–amino–2–(4–bromofenetil)benzo[f][1,7]naftiridin–8–il)metanol,

2–(4–metoxi–2–metilfenetil)–8–pentilbenzo[f][1,7]naftiridin–5–amina,

8–(2–ciclopropiletil)–2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–5–amina,

(5–amino–2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–8–il)metanol,

(5–amino–2–(4–propoxifenetil)benzo[f][1,7]naftiridin–8–il)metanol,

(2–(2–(1H–indol–5–il)etil)–5–aminobenzo[f][1,7]naftiridin–8–il)metanol,

metil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N,3–dimetilbenzamida,

N–(2–acetamidoetil)–4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamida,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N,3–dimetilbenzamida,

2–(4–metoxifenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–metoxi–2–metilfenetil)benzo[f][1,7]naftiridin–5–amina,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzamida,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N,N,3–trimetilbenzamida,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–hidroxietil)–3–metilbenzamida,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–3–metilbenzamida,

(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(pirrolidin–1–il)metanona,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dietilamino)etil)–3–metilbenzamida,

(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(4–etilpiperazin–1–il)metanona,

(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)(piperazin–1–il)metanona,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metil–N–(2–(pirrolidin–1–il)etil)benzamida,

4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N,3–dimetilbenzamida,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–N–(2–(dimetilamino)etil)–N–metilbenzamida,

2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol,

2–(4–butoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(2–(bifenil–4–il)etil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–((1,3–dihidroisobenzofuran–1–il)metil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

8–metil–2–(4–(2–metilaliloxi)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–(isopentiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil propil carbonato,

etil 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)pentanoato,

2–(4–(ciclopentiloxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(4–(ciclobutilmetoxi)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

8–metil–2–(4–(2–morfolinoetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)–1–feniletanona,

ácido 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)pentanoico,

2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)etanol,

2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)–N,N–dimetilacetamida,

8–metil–2–(2–metil–4–(2–morfolinoetoxi)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etanol,

dietil 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propilfosfonato,

ácido 3–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)propilfosfónico,

2–(4–butoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol,

2–(2–(4–(2–(5–aminobenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etanol,

etil 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)pentanoato,

ácido 5–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)pentanoico,

2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etanol,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil etil carbonato,

metil 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)butanoato,

ácido 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenoxi)butanoico,

ácido 4–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)butanoico,

2–(4–(isopentiloxi)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil hexil carbonato,

2–(2,4,6–trimetilfenetil)benzo[f][1,7]naftiridin–5–amina,

(5–amino–2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–8–il)metanol,

dietil 3–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)propilfosfonato,

dietil 3–(2–(2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenoxi)etoxi)etoxi)propilfosfonato,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil dimetilsulfamato,

(5–amino–2–(4–(dimetilamino)fenetil)benzo[f][1,7]naftiridin–8–il)metanol,

2–(4–(dimetilamino)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenol,

1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona,

2–(4–((dimetilamino)metil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(4–(1–(dimetilamino)etil)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanona oxima,

8–metil–2–(4–((metilamino)metil)fenetil)benzo[f][1,7]naftiridin–5–amina,

(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)bencilamino)etanol,

8–metil–2–(4–(pirrolidin–1–ilmetil)fenetil)benzo[f][1,7]naftiridin–5–amina,

2–(3,4–dimetoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)etanol,

1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etanol,

8–metil–2–(4–(oxazol–5–il)fenetil)benzo[f][1,7]naftiridin–5–amina,

3–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propanonitrilo,

(2R)–2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propan–1–ol,

8–metil–2–(4–(1–(piperazin–1–il)etil)fenetil)benzo[f][1,7]naftiridin–5–amina,

((2S)–1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidin–2–il)metanol,

N^1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^2,N^2–dimetiletano–1,2–diamina,

ácido 3–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)propanoico,

8–metil–2–(4–(1–(4–metilpiperazin–1–il)etil)fenetil)benzo[f][1,7]naftiridin–5–amina,

N^2–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^1,N^1–dimetilpropano–1,2–diamina,

8–metil–2–(4–(1–(2–(piridin–4–il)etilamino)etil)fenetil)benzo[f][1,7]naftiridin–5–amina,

N^1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)–N^2,N^2–dietiletano–1,2–diamina,

2–(4–(dimetilamino)–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina,

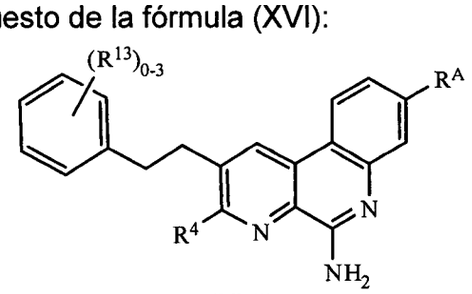
ácido 1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etil)pirrolidina–3–carboxílico,

4–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)fenil)etilamino)fenol,

1–(1–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2 il)etil)fenil)etil)pirrolidin–3–ol y

2–(4–(2–aminopropan–2–il)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

22. Un compuesto de la fórmula (XVI):



(XVI)

caracterizado porque cada R^4, R^A y R^{13} se selecciona de manera independiente de H, $–CH_3$, $–CH_2CH_3$, $–CF_3$, $–CH_2OH$, $–OCH_3$, $–COOCH_3$, $–COOCH_2CH_3$, F, Cl,

Br, $-CH_2OCH_3$, $CH_2OCH_2CH_3$, $-N(CH_3)_2$, $-((O(CH_2)_2)_{2-4}OH$, $-O(CH_2)_{2-4}-OH$, $-O(CH_2)_{2-4}-(PO_3H_2)$, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}-CH(CH_3)_2$, alquilo C_2-C_6 sustituido con 1-3 sustituyentes seleccionados de –OH, $-CH_3$, ciclopropilo, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}(PO_3H_2)$, –COOH, $COOCH_3$, y $-COOCH_2CH_3$;

o una de sus sales aceptables para uso farmacéutico.

23. El compuesto de la reivindicación 22, caracterizado porque R^4 es H.

24. El compuesto de la reivindicación 22 o de la reivindicación 23, caracterizado porque tiene uno a tres grupos R^{13}.

25. El compuesto de cualquiera de las reivindicaciones 22–24, caracterizado porque R^A es H o $-CH_3$.

26. El compuesto de cualquiera de las reivindicaciones 22–25, caracterizado porque tiene dos grupos R^{13} seleccionados del grupo que consiste en $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH_2OH$, $-OCH_3$, $-COOCH_3$, $-COOCH_2CH_3$, F, Cl, Br, $-CH_2OCH_3$, $CH_2OCH_2CH_3$, $-N(CH_3)_2$, $-((O(CH_2)_2)_{2-4}OH$, $-O(CH_2)_{2-4}-OH$, $-O(CH_2)_{2-4}-(PO_3H_2)$, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}-CH(CH_3)_2$, alquilo C_2-C_6 sustituido con 1-3 sustituyentes seleccionados de –OH, $-CH_3$, ciclopropilo, $-O(CH_2)_{2-4}-COOH$, $-O(CH_2)_{2-4}(PO_3H_2)$, –COOH, $COOCH_3$, y $-COOCH_2CH_3$.

27. El compuesto de la reivindicación 22, caracterizado porque es seleccionado de:

2–(4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilfenil)propan–2–ol;

2–(4–metoxi–2–metilfenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina;

2–(2,4–dimetilfenetil)benzo[f][1,7]naftiridin–5–amina;

etil 4–(2–(5–amino–8–metilbenzo[f][1,7]naftiridin–2–il)etil)–3–metilbenzoato;

2–(4–(dimetilamino)fenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina, y

2–(4–metoxifenetil)–8–metilbenzo[f][1,7]naftiridin–5–amina.

28. Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de cualquiera de las reivindicaciones 1–27 y un portador aceptable para uso farmacéutico.

29. Un medicamento para el tratamiento de una enfermedad o de un trastorno donde está implicada la modulación de un receptor TLR, caracterizado porque el medicamento comprende una cantidad terapéuticamente eficaz de un compuesto de cualquiera de las reivindicaciones 1–27.

30. El medicamento de la reivindicación 29, caracterizado porque el receptor TLR es TLR7.

31. El medicamento de la reivindicación 29, caracterizado porque el receptor TLR es TLR8.

32. El medicamento de la reivindicación 29, caracterizado porque el compuesto es un agonista de TLR.

33. El medicamento de la reivindicación 30, caracterizado porque el compuesto es un agonista de TLR7.

34. El medicamento de la reivindicación 31, caracterizado porque el compuesto es un agonista de TLR8.

35. Uso de un compuesto de cualquiera de las reivindicaciones 1–27, caracterizado porque en la elaboración de un medicamento para el tratamiento de una enfermedad o de un trastorno en un paciente, donde está implicada la modulación de un receptor TLR.

36. Un método para la modulación de un TLR, caracterizado porque comprende la administración a un sistema o un sujeto que lo necesita, de una cantidad terapéuticamente eficaz de un compuesto de cualquiera de las reivindicaciones 1–27, o de sus sales aceptables para uso farmacéutico o de sus composiciones farmacéuticas, para modular, de ese modo, el TLR.

37. Un método para el tratamiento de una enfermedad o de un trastorno donde está implicada la modulación de TLR, caracterizado porque comprende la administración a un sistema o un sujeto que necesita dicho tratamiento, de una cantidad eficaz de un compuesto de cualquiera de las reivindicaciones 1–27, o de sus sales aceptables para uso farmacéutico o de sus composiciones farmacéuticas, para, de ese modo, tratar la enfermedad o el trastorno.

38. El método de la reivindicación 36 o de la reivindicación 37, caracterizado porque el TLR es TLR7.

39. El método de la reivindicación 36 o de la reivindicación 37, caracterizado porque el TLR es TLR8.

40. El método de la reivindicación 36 o de la reivindicación 37, caracterizado porque el compuesto es un agonista de TLR.

41. El método de la reivindicación 36 o de la reivindicación 37, caracterizado porque el compuesto es un agonista de TLR7.

42. El método de la reivindicación 36 o de la reivindicación 37, caracterizado porque el compuesto es un agonista de TLR8.

43. El método de cualquiera de las reivindicaciones 36–42, caracterizado porque comprende la administración del compuesto a un sistema de tejido o una célula, o a un sujeto animal o humano.

44. El método de la reivindicación 37, caracterizado porque la enfermedad o afección es una enfermedad infecciosa, una enfermedad inflamatoria, una enfermedad respiratoria, una enfermedad dermatológica o una enfermedad autoinmunitaria.

45. El método de la reivindicación 44, caracterizado porque la enfermedad o afección es asma, enfermedad pulmonar obstructiva crónica (EPOC), síndrome de insuficiencia respiratoria del adulto (ARDS), colitis ulcerosa, enfermedad de Crohn, bronquitis, dermatitis, queratosis actínica, carcinoma de

célula basal, rinitis alérgica, soriasis, esclerodermia, urticaría, artritis reumatoide, esclerosis múltiple, cáncer, cáncer de mama, HIV o lupus.

46. Un método para el tratamiento de una enfermedad proliferativa celular, caracterizado porque comprende la administración a un sistema o a un sujeto que necesita dicho tratamiento, de una cantidad eficaz de un compuesto de cualquiera de las reivindicaciones 1–27, o de sus sales aceptables para uso farmacéutico, o de sus composiciones farmacéuticas, donde la enfermedad proliferativa celular es linfoma, osteosarcoma, melanoma o un tumor de mama, renal, próstata, colorrectal, tiroideo, ovárico, pancreático, neuronal, pulmonar, uterino o gastrointestinal.

47. Una composición farmacéutica caracterizada porque comprende un compuesto de cualquiera de las reivindicaciones 1–27, un antígeno y un portador aceptable para uso farmacéutico, donde la composición farmacéutica es una composición inmunógena, y el compuesto es un potenciador inmunológico.

48. La composición farmacéutica de la reivindicación 47, caracterizada porque la composición farmacéutica además comprende un agente inmunorregulador adicional.

49. La composición farmacéutica de la reivindicación 47, caracterizada porque el agente inmunorregulador adicional es un coadyuvante seleccionado de una composición que contiene minerales, una emulsión oleosa, una formulación de saponina, un virosoma, una partícula de tipo viral, un derivado bacteriano, un derivado microbiano, un inmunomodulador humano, un bioadhesivo, un mucoadhesivo, una micropartícula, un liposoma, una formulación de polioxietileno éter, una formulación de polioxietileno éster, un polifosfazeno, un péptido de muramilo, o un compuesto de imidazoquinolona.

50. La composición farmacéutica de la reivindicación 49, caracterizada porque el coadyuvante es una emulsión oleosa.

51. La composición farmacéutica de cualquiera de las reivindicaciones 47–50, caracterizada porque el compuesto se presenta en una cantidad suficiente para producir un efecto inmunoestimulante con la administración.

52. Un método para mejorar la eficacia de una composición inmunógena, caracterizado porque comprende la adición de una cantidad eficaz de un compuesto de acuerdo con una de las reivindicaciones 1–27, a la composición inmunógena.

53. Una composición inmunógena que comprende un compuesto de cualquiera de las reivindicaciones 22–27 y un antígeno, caracterizada porque la cantidad del compuesto es una cantidad eficaz para mejorar una respuesta inmunitaria al antígeno en un sujeto al cual se administra la composición.

54. La composición inmunógena de la reivindicación 53, caracterizada porque el antígeno es un antígeno bacteriano.

55. La composición inmunógena de la reivindicación 54, caracterizada porque el antígeno bacteriano es un antígeno de una cepa de *Neisseria meningitides.*

56. La composición inmunógena de la reivindicación 53, caracterizada porque el antígeno es un antígeno viral o un antígeno fúngico.

57. La composición inmunógena de la reivindicación 53, caracterizada porque además comprende un coadyuvante adicional.

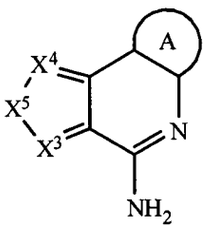
58. La composición inmunógena de cualquiera de las reivindicaciones 53–57, caracterizada porque el antígeno es un polipéptido.

59. La composición inmunógena de la reivindicación 58, caracterizado porque el polipéptido tiene por lo menos 85% de identidad con respecto a una secuencia seleccionada del grupo que consiste en SEC. ID. NROS.: 1–6.

p.p.de: IRM LLC * NOVARTIS AG

RESUMEN

Un compuesto de la Fórmula (I–A), o una sal aceptable para uso farmacéutico o un solvato aceptable para uso farmacéutico de dicho compuesto:



Fórmula (I–A)

donde:

X^3 es N;

X^4 es N o CR^3;

X^5 es $–CR^4=CR^5–$;

R^3 es H;

R^4 y R^5 se seleccionan, de manera independiente, de H, halógeno, $–C(O)OR^7$, $–C(O)R^7$, $–C(O)N(R^{11}R^{12})$, $–N(R^{11}R^{12})$, $–N(R^9)_2$, $–NHN(R^9)_2$, $–SR^7$, $–(CH_2)_nOR^7$, $–(CH_2)_nR^7$, $–LR^8$, $–LR^{10}$, $–OLR^8$, $–OLR^{10}$, alquilo $C_1–C_6$, heteroalquilo $C_1–C_6$, haloalquilo $C_1–C_6$, alqueno $C_2–C_8$, alquino $C_2–C_8$, alcoxi $C_1–C_6$, haloalcoxi $C_1–C_6$, arilo, heteroarilo, cicloalquilo $C_3–C_8$ y heterocicloalquilo $C_3–C_8$, donde los grupos alquilo $C_1–C_6$, heteroalquilo $C_1–C_6$, haloalquilo $C_1–C_6$, alqueno $C_2–C_8$, alquino $C_2–C_8$, alcoxi $C_1–C_6$, haloalcoxi $C_1–C_6$, arilo, heteroarilo, cicloalquilo $C_3–C_8$ y heterocicloalquilo $C_3–C_8$ de R^4 y R^5, de manera independiente, están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de modo independiente de halógeno, –CN, $-NO_2$, $–R^7$, $–OR^8$, $–C(O)R^8$, $–OC(O)R^8$, $–C(O)OR^8$, $–N(R^9)_2$, $–P(O)(OR^8)_2$, $–OP(O)(OR^8)_2$, $–P(O)(OR^{10})_2$, $–OP(O)(OR^{10})_2$, $–C(O)N(R^9)_2$, $–S(O)_2R^8$, $–S(O)R^8$, $–S(O)_2N(R^9)_2$ y $–NR^9S(O)_2R^8$;

o R^3 y R^4, o R^4 y R^5, cuando se presentan en átomos de anillo adyacentes, pueden estar opcionalmente ligados para formar un anillo de 5–6 miembros, donde el anillo de 5-6 miembros está opcionalmente sustituido con R^7;

cada L se selecciona de manera independiente de un enlace, $-(O(CH_2)_m)_t-$, alquilo C_1–C_6, alquenileno C_2–C_6 y alquinileno C_2–C_6, donde los grupos alquilo C_1–C_6, alquenileno C_2–C_6 y alquinileno C_2–C_6 de L están, cada uno, opcionalmente sustituidos con 1 a 4 sustituyentes seleccionados independientemente de halógeno, $-R^8$, $-OR^8$, $-N(R^9)_2$, $-P(O)(OR^8)_2$, $-OP(O)(OR^8)_2$, $-P(O)(OR^{10})_2$, y $-OP(O)(OR^{10})_2$;

R^7 se selecciona de H, alquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6 y heterocicloalquilo C_3–C_8, donde los grupos alquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alqueno C_2–C_8, alquino C_2–C_8, alcoxi C_1–C_6, haloalcoxi C_1–C_6 y heterocicloalquilo C_3–C_8 de R^7, de manera independiente, están opcionalmente sustituidos con 1 a 3 grupos R^{13}, y cada R^{13} se selecciona de modo independiente de halógeno, –CN, $-LR^9$, $-LOR^9$, $-OLR^9$, $-LR^{10}$, $-LOR^{10}$, $-OLR^{10}$, $-LR^8$, $-LOR^8$, $-OLR^8$, $-LSR^8$, $-LSR^{10}$, $-LC(O)R^8$, $-OLC(O)R^8$, $-LC(O)OR^8$, $-LC(O)R^{10}$, $-LOC(O)OR^8$, $-LC(O)NR^9R^{11}$, $-LC(O)NR^9R^8$, $-LN(R^9)_2$, $-LNR^9R^8$, $-LNR^9R^{10}$, $-LC(O)N(R^9)_2$, $-LS(O)_2R^8$, $-LS(O)R^8$, $-LC(O)NR^8OH$, $-LNR^9C(O)R^8$, $-LNR^9C(O)OR^8$, $-LS(O)_2N(R^9)_2$, $-OLS(O)_2N(R^9)_2$, $-LNR^9S(O)_2R^8$, $-LC(O)NR^9LN(R^9)_2$, $-LP(O)(OR^8)_2$, $-LOP(O)(OR^8)_2$, $-LP(O)(OR^{10})_2$ y $-OLP(O)(OR^{10})_2$;

cada R^8 se selecciona de manera independiente de H, $-CH(R^{10})_2$, alquilo C_1–C_8, alqueno C_2–C_8, alquino C_2–C_8, haloalquilo C_1–C_6, alcoxi C_1–C_6, heteroalquilo C_1–C_6, cicloalquilo C_3–C_8, heterocicloalquilo C_2–C_8, hidroxialquilo C_1–C_6, y haloalcoxi C_1–C_6, donde los grupos alquilo C_1–C_8, alqueno C_2–C_8, alquino C_2–C_8, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, alcoxi C_1–C_6, cicloalquilo

C_3–C_8, heterocicloalquilo C_2–C_8, hidroxialquilo C_1–C_6 y haloalcoxi C_1–C_6 de R^8 están, cada uno, opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente de –CN, R^{11}, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-OC(O)R^{11}$, $-C(O)N(R^9)_2$, $-C(O)OR^{11}$, $-NR^9C(O)R^{11}$, $-NR^9R^{10}$, $-NR^{11}R^{12}$, $-N(R^9)_2$, $-OR^9$, $-OR^{10}$, $-C(O)NR^{11}R^{12}$, $-C(O)NR^{11}OH$, $-S(O)_2R^{11}$, $-S(O)R^{11}$, $-S(O)_2NR^{11}R^{12}$, $-NR^{11}S(O)_2R^{11}$, $-P(O)(OR^{11})_2$, y $-OP(O)(OR^{11})_2$;

cada R^9 se selecciona de manera independiente de H, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-S(O)_2R^{10}$, alquilo C_1–C_6, heteroalquilo C_1–C_6 y cicloalquilo C_3–C_6; o cada R^9 es, de modo independiente, un alquilo C_1–C_6 que junto con N, se une para formar un heterocicloalquilo C_3–C_8, donde el anillo heterocicloalquilo C_3–C_8 contiene opcionalmente un heteroátomo adicional seleccionado de N, O y S, y donde los grupos alquilo C_1–C_6, heteroalquilo C_1–C_6, cicloalquilo C_3–C_6, o heterocicloalquilo C_3–C_8 de R^9 están, cada uno, opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente de –CN, R^{11}, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-OC(O)R^{11}$, $-C(O)OR^{11}$, $-NR^{11}R^{12}$, $-C(O)NR^{11}R^{12}$, $-C(O)NR^{11}OH$, $-S(O)_2R^{11}$, $-S(O)R^{11}$, $-S(O)_2NR^{11}R^{12}$, $-NR^{11}S(O)_2R^{11}$, $-P(O)(OR^{11})_2$, y $-OP(O)(OR^{11})_2$;

cada R^{10} se selecciona de manera independiente de arilo, cicloalquilo C_3–C_8, heterocicloalquilo C_3–C_8 y heteroarilo, donde los grupos arilo, cicloalquilo C_3–C_8, heterocicloalquilo C_3–C_8 y heteroarilo están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de halógeno, $-R^8$, $-OR^8$, $-LR^9$, $-LOR^9$, $-N(R^9)_2$, $-NR^9C(O)R^8$, $-NR^9CO_2R^8$, $-CO_2R^8$, $-C(O)R^8$ y $-C(O)N(R^9)_2$;

R^{11} y R^{12} se seleccionan de manera independiente de H, alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8, donde los grupos alquilo C_1–C_6, heteroalquilo C_1–C_6, haloalquilo C_1–C_6, arilo, heteroarilo, cicloalquilo C_3–C_8 y heterocicloalquilo C_3–C_8 de R^{11} y R^{12}, de modo independiente, están opcionalmente sustituidos con 1 a 3

sustituyentes seleccionados de manera independiente de halógeno, –CN, R^8, $–OR^8$, $–C(O)R^8$, $^-OC(O)R^8$, $–C(O)OR^8$, $–N(R^9)_2$, $–NR^8C(O)R^8$, $–NR^8C(O)OR^8$, $–C(O)N(R^9)_2$, heterocicloalquilo C_3–C_8, $–S(O)_2R^8$, $–S(O)_2N(R^9)_2$, $–NR^9S(O)_2R^8$, haloalquilo C_1–C_6 y haloalcoxi C_1–C_6;

o R^{11} y R^{12} son, de manera independiente, alquilo C_1–C_6, y tomados junto con el átomo de N al cual están unidos forman un anillo heterocicloalquilo C_3–C_8 opcionalmente sustituido, que contiene opcionalmente un heteroátomo adicional seleccionado de N, O y S;

el anillo A es un arilo o un heteroarilo, donde los grupos arilo y heteroarilo del anillo A están opcionalmente sustituidos con 1 a 3 grupos R^A, donde cada R^A se selecciona de manera independiente de $–R^8$, $–R^7$, $–OR^7$, $–OR^8$, $–R^{10}$, $–OR^{10}$, $–SR^8$, $–NO_2$, –CN, $–N(R^9)_2$, $–NR^9C(O)R^8$, $–NR^9C(S)R^8$, $–NR^9C(O)N(R^9)_2$, $–NR^9C(S)N(R^9)_2$, $–NR^9CO_2R^8$, $–NR^9NR^9C(O)R^8$, $–NR^9NR^9C(O)N(R^9)_2$, $–NR^9NR^9CO_2R^8$, $–C(O)C(O)R^8$, $–C(O)CH_2C(O)R^8$, $–CO_2R^8$, $–(CH_2)_nCO_2R^8$, $–C(O)R^8$, $–C(S)R^8$, $–C(O)N(R^9)_2$, $–C(S)N(R^9)_2$, $–OC(O)N(R^9)_2$, $–OC(O)R^8$, $–C(O)N(OR^8)R^8$, $–C(NOR^8)R^8$, $–S(O)_2R^8$, $–S(O)_3R^8$, $–SO_2N(R^9)_2$, $–S(O)R^8$, $–NR^9SO_2N(R^9)_2$, $–NR^9SO_2R^8$, $–P(O)(OR^8)_2$, $–OP(O)(OR^8)_2$, $–P(O)(OR^{10})_2$, $–OP(O)(OR^{10})_2$, $–N(OR^8)R^8$, $–CH=CHCO_2R^8$, $–C(=NH)–N(R^9)_2$ y $–(CH_2)_nNHC(O)R^8$; o dos sustituyentes R^A adyacentes en el anillo A forman un anillo de 5–6 miembros que contiene hasta dos heteroátomos como miembros de anillo; y

n es, de manera independiente en cada aparición, 0; 1; 2; 3; 4; 5; 6; 7 u 8; cada m se selecciona de manera independiente de 1; 2; 3; 4; 5 y 6, y

t es 1; 2; 3; 4; 5; 6; 7 u 8.

También se dan a conocer composiciones farmaceuticas y medicamentos que los comprenden, métodos para modular un LTR, métodos para tratar una

FIGURA 1

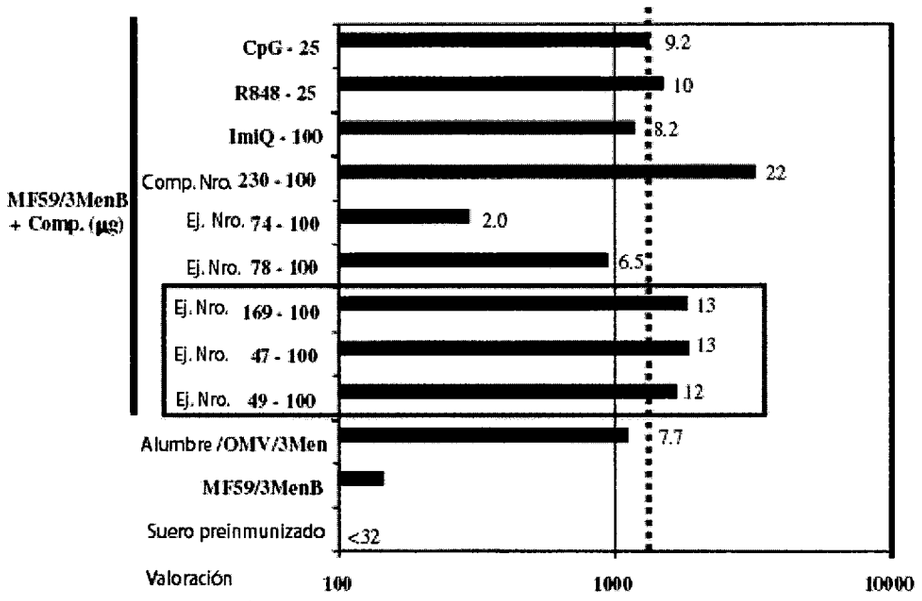

MF59/3MenB + Comp. (µg)
CpG - 25
R848 - 25
ImiQ - 100
Comp. Nro. 230 - 100
Ej. Nro. 74 - 100
Ej. Nro. 78 - 100
Ej. Nro. 169 - 100
Ej. Nro. 47 - 100
Ej. Nro. 49 - 100
Alumbre /OMV/3Men
MF59/3MenB
Suero preinmunizado
Valoración
9.2
10
8.2
22
2.0
6.5
13
13
12
7.7
<32
100
1000
10000

FIGURA 2

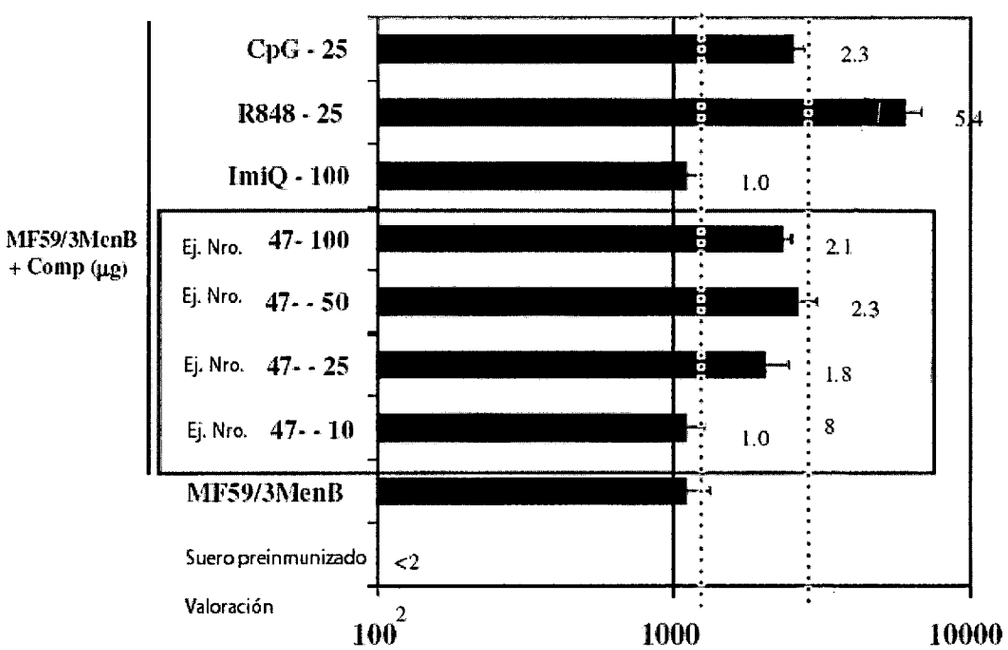

MF59/3MenB + Comp (µg)
CpG - 25
R848 - 25
ImiQ - 100
Ej. Nro. 47- 100
Ej. Nro. 47- - 50
Ej. Nro. 47- - 25
Ej. Nro. 47- - 10
MF59/3MenB
Suero preinmunizado
Valoración
2.3
5.4
1.0
2.1
2.3
1.8
1.0
8
<2
100
2
1000
10000

FIGURA 3

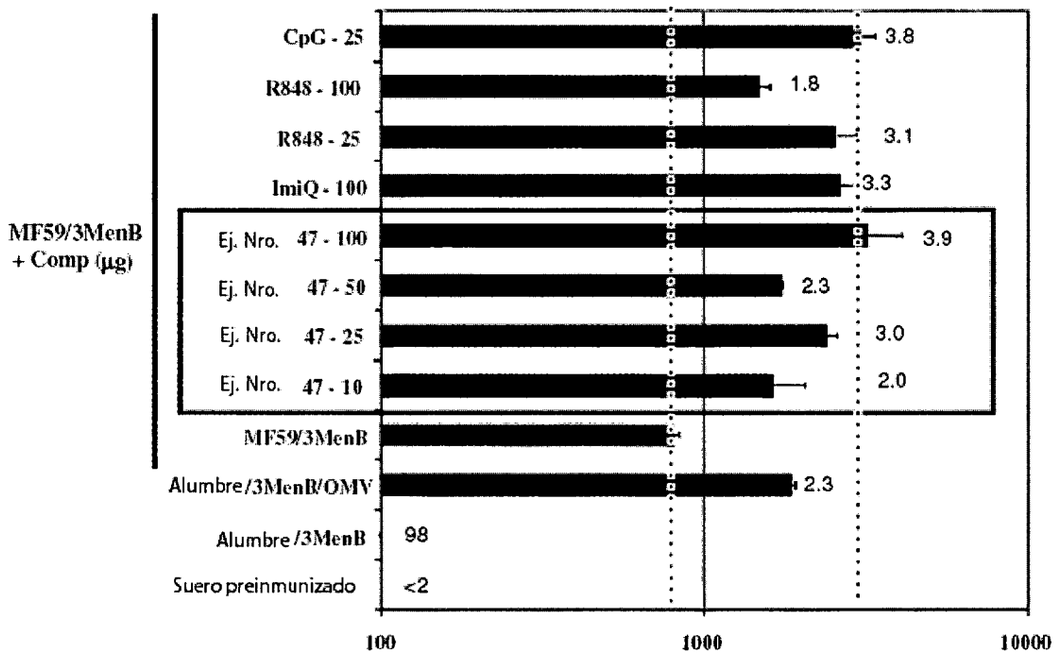

MF59/3MenB + Comp (µg)
CpG - 25
R848 - 100
R848 - 25
ImiQ - 100
Ej. Nro. 47 - 100
Ej. Nro. 47 - 50
Ej. Nro. 47 - 25
Ej. Nro. 47 - 10
MF59/3MenB
Alumbre/3MenB/OMV
Alumbre/3MenB
Suero preinmunizado
3.8
1.8
3.1
3.3
3.9
2.3
3.0
2.0
2.3
98
<2
100
1000
10000

FIGURA 4

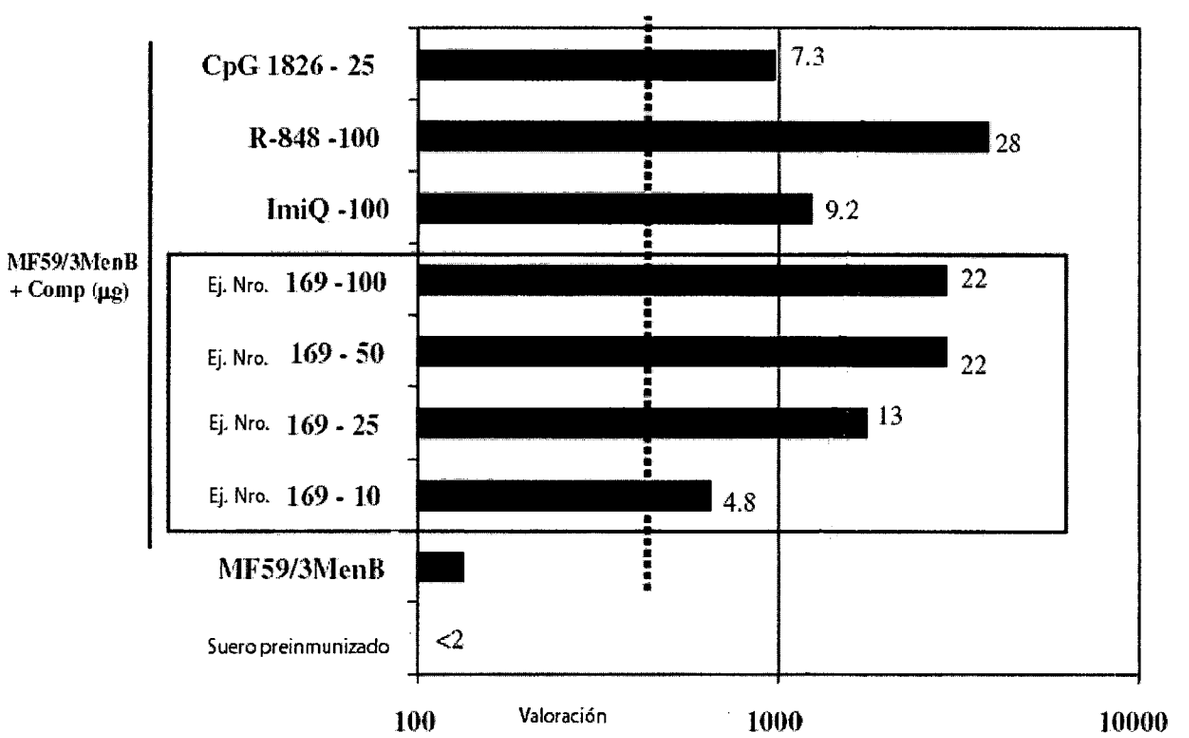
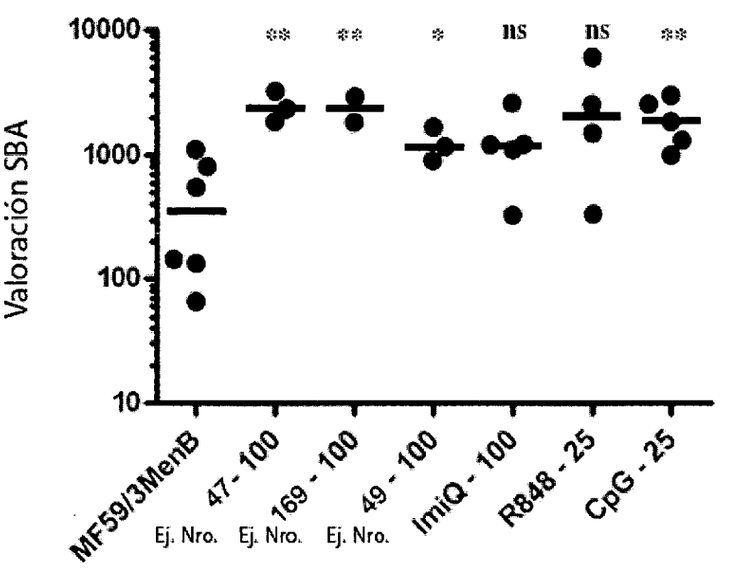

MF59/3MenB + Comp (µg)
CpG 1826 - 25
R-848 -100
ImiQ -100
Ej. Nro. 169 -100
Ej. Nro. 169 - 50
Ej. Nro. 169 - 25
Ej. Nro. 169 - 10
MF59/3MenB
Suero preinmunizado
7.3
28
9.2
22
22
13
4.8
<2
100
Valoración
1000
10000

FIGURA 5

Resumen de información SBA MenB
(6 experimentos)



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference P1326PC20	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2009/035563	International filing date *(day/month/year)* 27 February 2009 (27.02.2009)	Priority date *(day/month/year)* 03 March 2008 (03.03.2008)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant IRM LLC		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. 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

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 07 September 2010 (07.09.2010)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Simin Baharlou e-mail: pt09.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

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From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2009/035563	27.02.2009	03.03.2008

International Patent Classification (IPC) or both national classification and IPC
INV. C07D221/12 C07D471/04 C07D471/12 C07D491/056 C07D491/12 C07D495/04 A61K31/4375 A61P37/04

Applicant
IRM LLC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ 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 Rule 43*bis*.1(a)(i) 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

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Gutke, Hans-Jürgen Telephone No. +49 89 2399-5633

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US2009/035563

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ 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 (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☒ on paper

      ☒ in electronic form

   c. time of filing/furnishing:

      ☒ contained in the international application as filed.

      ☒ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,5,6,12,15,21-59
	No:	Claims	1,3,4,7-11,13,14,16-20
Inventive step (IS)	Yes:	Claims	5,12,15,21-27
	No:	Claims	1-4,7-11,13,14,16-59
Industrial applicability (IA)	Yes:	Claims	1-59
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

1 Reference is made to the following documents:

D1: US-A-5 741 909 (GERSTER JOHN F [US] ET AL) 21 April 1998 (1998-04-21)

D2: WO 2007/109813 A (NOVARTIS AG [CH]; SUTTON JAMES [US]; XU FENG [US]; VALIANTE NICHOLAS [) 27 September 2007 (2007-09-27)

D3: FERRARIS DANA ET AL: "Design and synthesis of poly ADP-ribose polymerase-1 inhibitors. 2. Biological evaluation of aza-5(H)-phenanthridin-6-ones as potent, aqueous-soluble compounds for the treatment of ischemic injuries." JOURNAL OF MEDICINAL CHEMISTRY, vol. 46, no. 14, 3 July 2003 (2003-07-03), pages 3138-3151, XP002531095 ISSN: 0022-2623

2 Claims 36-46 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

3 **Novelty**

3.1 The present application relates to condensed amino naphthyridines (cf. claims 1-27), their corresponding pharmaceutical compositions and method to prepare said compositions (cf. claims 28-34, 47-59) and the medical use e.g. as immune stimulant (cf. claims 35-46).

3.2 D1 relates to benzo fused amino **imidazo** pyridines (cf. D1, column 2, formula I), their pharmaceutical composition and medical use as immune stimulant for the treatment of inflammatory and proliferative disorders and viral infections (cf. D1, column 11, lines 38-65). The compounds of D1 differ from the present compounds which all are fused amino **pyrido** or **pyrazino** pyridines. Thus the compounds

according to present claims 1-27 are novel vis à vis D1. Consequently present claims 28-34 and 47-59 (composition) and claims 35-46 (medical use) are also novel vis à vis D1.

3.3 D2 relates to benzo fused amino **imidazo pyrazines** (cf. D2, claim 1), their corresponding pharmaceutical composition (cf. D2, claim 57) and their medical use as immune modulator for the treatment of allergic and proliferative diseases and viral and bacterial infections (cf. D2, claims 25-39). The compounds of D2 differ from the present compounds which are all fused amino **pyrido** or **pyrazino** pyridines. Thus the compounds according to present claims 1-27 are novel vis à vis D2. Consequently present claims 28-34 and 47-59 (composition) and claims 35-46 (medical use) are also novel vis à vis D2.

3.4 D3 discloses i.a. a specific compound (cf. D3, page 3139, compound 12) which anticipates present claims 1, 3, 4, 7-11, 13, 14 and 16-20. Claims 2, 5, 6, 12, 15, 20 and 22-27 are novel because they differ with regard to the substituents R4/R5 or the ring A from the compound of D3. The list of specific compounds of claim 21 is novel vis à vis the specific compound of D3. Since the relevant compound is described in D3 as an intermediary compound, present claims 28-34 and 47-59 (composition) and claims 35-46 (medical use) are also novel vis à vis D3.

4 **Inventive Step** (relating to new subject-matter)

4.1 D1 may be regarded as closest prior art since this document describes compounds with the same qualitative activity as the present compounds, namely as immune stimulant for the treatment of infectious diseases and cancer. The present compounds result from either the insertion of an additional carbon atom into the imidazole ring (compounds where X4 is nitrogen) or from the insertion of a carbon into the imidazole ring **and** the exchange of one nitrogen for a carbon atom (compounds where X4 is carbon). The objective problem is seen in the provision of further immune stimulating compounds.

4.2 The applicant provides compounds according to claims 1-27. For a number of specific compounds biological activity within a certain range is disclosed (cf. page 326-334, paragraph 827) without specifying which test has been used. For a

smaller number of specific compounds a specific activity in specific tests is described (cf. page 335-336, paragraphs 829-836). It is considered that D1 (or D2) would not have induced the skilled person to find the present solution of the problem, namely the ring modification leading to the present compounds. However, claims 1 and 2 contain an unlimited definition for ring A. It is not likely that substantially all compounds of these claims can solve the problem. For novel claims 5, 12, 15 and 22-27 inventive step could be acknowledged. For novel claims 28-59, when dependent from claims 1 or 2, inventive step is not acknowledged at present.

Re Item VII

5.1 The description contains embodiments which are either not novel (cf. example 1) or not covered by the claims (cf. examples 39; and table 1, compounds 3, 5, 6, 55, 58-64). These compounds should be either indicated as reference compounds or deleted from the description, so that no unclarity arises with regard to the scope of the protection desired.

5.2 The vague and imprecise statement in the description on page 336, paragraph 837 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them.

Re Item VIII

6.1 Claim 1 contains definitions for R1 and R2. Since the compounds of formula I-A do not contain such residues R1 and R2, these definitions are redundant.

6.2 Independent claims 36-46 and 51-59 contain a feature, namely "amount effective to ...", which is regarded as an effect to be achieved. This feature does not give any indication for the skilled reader to exercise the invention. The claims are regarded as unclear.

6.3 Claims 29-35 and 37-43 do not meet the requirements of Article 6 PCT for the

following reasons. The therapeutic application of the products is functionally defined by a mechanism of action (i.e. by their capability of modulating TLR), which does not allow any practical application in the form of a defined, real treatment of a pathological condition. The objection could be overcome by introducing in the claims a list of pathological conditions (diseases) cited in the application.

PATENT COOPERATION TREATY

PCT/US2009/035563

ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

RAYMOND, Daniel, E.
Genomics Institute of the Novartis Research Foundation
10675 John Jay Hopkins Drive
San Diego, CA 92121
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)* 09 August 2010 (09.08.2010)	
Applicant's or agent's file reference P1326PC20	IMPORTANT NOTIFICATION
International application No. PCT/US2009/035563	International filing date *(day/month/year)* 27 February 2009 (27.02.2009)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
IRM LLC 131 Front Street P.O. Box 2899 HM LX Hamilton Bermuda	US	US
	Telephone No. 858-812-1539	
	Facsimile No. 858-812-1909	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
IRM LLC 131 Front Street P.O. Box HM 2899 HM LX Hamilton Bermuda	US	US
	Telephone No. 858-812-1539	
	Facsimile No. 858-812-1909	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Perez Roberto
Facsimile No. +41 22 338 71 30	e-mail pt09.pct@wipo.int Telephone No. +41 22 338 74 09

Form PCT/IB/306 (January 2009) I/EJ07827B0

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Name and Address	State of Nationality	State of Residence
WU, Tom Yao-Hsiang 9175 Judicial Drive San Diego, CA 92122 United States of America	CA	US
	Telephone No.	
	Facsimile No.	
	E-mail address	

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Name and Address	State of Nationality	State of Residence
WU, Tom Yao-Hsiang 9175 Judicial Drive Unit 6514 San Diego, CA 92122 United States of America	US	US
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Name and Address	State of Nationality	State of Residence
LI, Yongkai 935 Babauta Road, Unit 7 San Diego, CA 92129 United States of America	CN	US
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

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Name and Address	State of Nationality	State of Residence
LI, Yongkai 9325 Babauta Road, Unit 7 San Diego, CA 92129 United States of America	US	US
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Name and Address
CORTEZ, Alex
4073 Kendall Street, Apt.C
San Diego, CA 92109
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
CORTEZ, Alex
12702 Torrey Bluff Drive
Apt. 191
San Diego, CA 92130
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
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Name and Address
ZOU, Yefen
3420 Lebon Drive
San Diego, CA 92122
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State of Nationality: CN
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

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Name and Address
ZOU, Yefen
8730 Costa Verde Blvd.
San Diego, CA 92122
United States of America

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Applicant's or agent's file reference: P1326PC20	**IMPORTANT NOTIFICATION**
International application No.: PCT/US2009/035563	International filing date *(day/month/year)*: 27 February 2009 (27.02.2009)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
ZHANG, Xiaoyue 7698 Palmilla Drive, Apt. 1113 San Diego, CA 92122 United States of America	CN	US
	Telephone No.	
	Facsimile No.	
	E-mail address	

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Name and Address	State of Nationality	State of Residence
ZHANG, Xiaoyue 4121 Via Candidiz Unit 43 San Diego, CA 92130 United States of America	CN	US
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1211 Geneva 20, Switzerland

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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-122816- -00000-0000
Fecha: 2010-10-04 17:10:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 522

PATENTE DE INVENCIÓN ☐ **MODELO DE UTILIDAD** ☐

- ☐ Indicación que se solicita 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 (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☑ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita 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 ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
NOVARTIS AG

REFERENCIA	Radicación No.	10 122816
	Solicitud internacional	PCT/US2009/035563
	Fecha inicio fase nacional	03/10/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	14359

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Continua en la página siguiente...

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5 , 7 y 10 PBX: 5870000
Sede CAN: Av. Cra 50 No. 26-55 int. 2 Tel: 5880070
Call Center 6513240. Línea 01800-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 05 NOV. 2010.
adpa11

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
NOVARTIS AG

REFERENCIA	Radicación No.	10 122816
	Solicitud internacional	PCT/US2009/035563
	Fecha inicio fase nacional	03/10/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	№ 14360

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 05 NOV. 2010
adpa11