PCT

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARI

DELEGATURA DE PROPIE
DIRECCIÓN DE NUEVAS

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-153711- -00000-0000
Fecha: 2010-12-06 17:39:02 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 455

SOLICITUD DE PATENTE DE INVENCIÓN

10-153711

TITULO: HETEROCICLICOS QUE CONTIENEN NITRÓGENO FUSIONADO Y COMPOSICIONES DE LOS MISMOS COMO INHIBIDORES DE CINASA

SOLICITANTE: IRM LLC

DIRECCIÓN: 131 Front Street, P.O. Box HM 2899, Hamilton HM LX, Bermuda

APODERADO: CARLOS R. OLARTE

BOGOTÁ 6 de Diciembre de 2010

P2010/000173

Titul. Cw
13-12-2010

OLARTERAISBECK
OLARTE RAISBECK MOURE & CASTRO LTDA.

Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación.

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2010/000173**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: IRM LLC
Dirección: 131 Front Street, P.O. Box HM 2899, Hamilton HM LX, Bermuda
Nacionalidad o Domicilio: Bermuda
Lugar de Constitución: Bermuda
Teléfono: _____ **Fax:** _____
E-mail: _____

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

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: Diagonal 34 No. 5-28 Bogotá, Colombia
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/US2009/043073 Fecha Mayo 7, 2009

Publicación Internacional No. WO 2009/140128 Fecha Noviembre 19, 2009

(6) **Título (54) HETEROCICLICOS QUE CONTIENEN NITRÓGENO FUSIONADO Y COMPOSICIONES DE LOS MISMOS COMO INHIBIDORES DE CINASA** (folios 460)

Clasificación Internacional (51) C07D 471/04, C07D 487/04, A61K 31/4985, A61K 31/5353 A61P 37/00

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

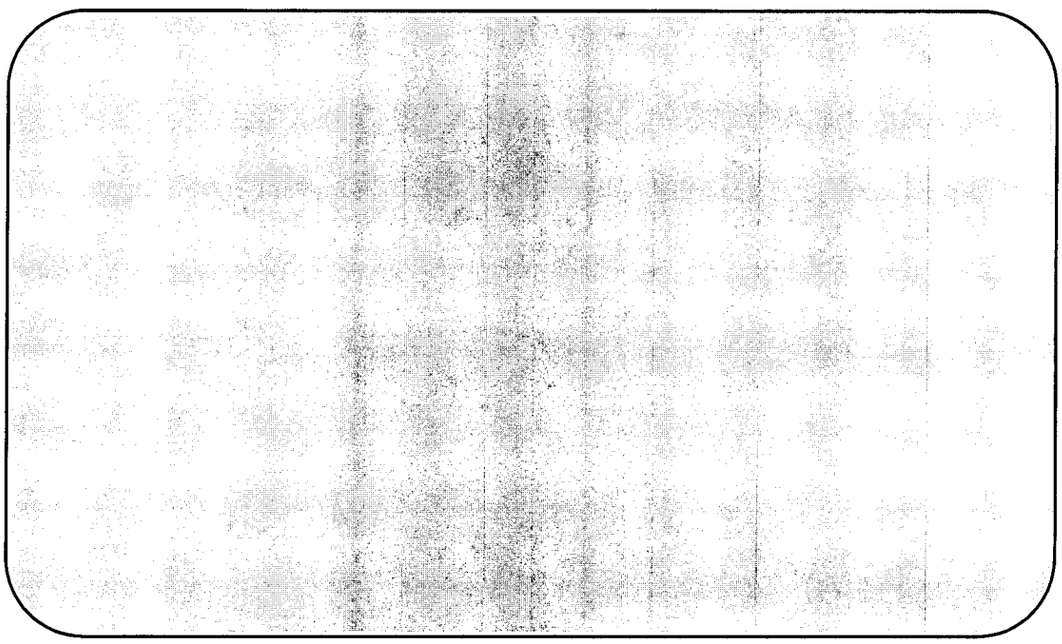
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Mayo 13, 2008	61/052.879
US	Febrero 16, 2009	61/152.872

(9) **Comprobante de pago No.** 10-102,802 **Fecha** Diciembre 2, 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. 06-124.397
- [ ] 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).
- [ ] 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.
- [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/US2009/043073

1. **Pamela A. ALBAUGH,**
   6081 Paseo Monona,
   Carlsbad, CA 92009
   Estados Unidos
   Nacionalidad: Estadounidense

2. **Ha-Soon CHOI,**
   13716 Fontanelle Plaec,
   San Diego, CA 92128
   Estados Unidos
   Nacionalidad: Koreana

3. **Gregory CHOPIUK,**
   2055 Pendrell Street,
   Suite 803 Vancouver, British Columbia
   V6G 1T9
   Canada
   Nacionalidad: Canadiense

4. **Yi FAN,**
   12228 Pepper Tree Lane,
   Poway, CA 92064
   Glen Way, Apt. 101,
   Carlsbad, CA 92008
   Estados Unidos
   Nacionalidad: Estadounidense

5. **Paul Vincent RUCKER,**
   2390 Rising Glen Way, Apt. 101,
   Carlsbad, CA 92008
   Estados Unidos
   Nacionalidad: Estadounidense

6. **Zhicheng WANG,**
   13012 Chambord Way,
   San Diego, CA 92130
   Estados Unidos
   Nacionalidad: China

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-153711- -00000-0000
Fecha: 2010-12-06 17:39:02 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 455

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 102,802
FECHA : DICIEMBRE 2 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	396432632	02/12/2010	2,874,000.00

***** 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

5

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

6

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: "JRM 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

MINISTERIO DE
RELACIONES EXTERIORES

2010 ENE 29 A 11:43

JEFE DE LEGALIZACIONES
BOGOTA D.C.

NO SE ASUME
RESPONSABILIDAD
DEL TEXTO

006900

Jorge Sierra
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
AS FUNCIONES INDICADAS

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 Alva
Gina A
Juan Felipe Ac
Andrés Rin
Grace G
Mariana Fra
Of Co
Guillermo Ch
Graciela M
Jacqueline Chap
Cruz E. de Moncal

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

4

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 *

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

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 November 2009 (19.11.2009)

PCT

(10) International Publication Number
WO 2009/140128 A2

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61K 31/4353* (2006.01)
C07D 487/04 (2006.01) *A61P 37/00* (2006.01)
A61K 31/4985 (2006.01)

(21) International Application Number:
PCT/US2009/043073

(22) International Filing Date:
7 May 2009 (07.05.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/052,879 13 May 2008 (13.05.2008) US
61/152,872 16 February 2009 (16.02.2009) US

(71) Applicant *(for all designated States except US)*: **IRM LLC** [US/US]; 131 Front Street, P.O, Box 2899, Bermuda, Hamilton, HM LX (BM).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ALBAUGH, Pamela, A.** [US/US]; 6081 Paseo Monona, Carlsbad, CA 92009 (US). **CHOI, Ha-Soon** [KR/US]; 13716 Fontanelle Place, San Diego, CA 92128 (US). **CHOPIUK, Gregory** [CA/US]; 10994 West Ocean Air Drive, Apt. 387, San Diego, CA 92130 (US). **FAN, Yi** [CN/US]; 12228 Pepper Tree Lane, Poway, CA 92064 (US). **RUCKER, Paul, Vincent** [US/US]; 2390 Rising Glen Way, Apt. 101, Carlsbad, CA 92008 (US). **WANG, Zhicheng** [CN/US]; 13012 Chambord Way, San Diego, CA 92130 (US).

(74) Agents: **RAYMOND, Daniel, E.** et al.; Genomics Institute of the Novartis Research Foundation, 10675 John Jay Hopkins Drive, San Diego, CA 92121 (US).

(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, 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:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) **Title**: COMPOUNDS AND COMPOSITIONS AS KINASE INHIBITORS

(57) **Abstract**: The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with abnormal or deregulated kinase activity, particularly Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and ALK or combinations thereof.

WO 2009/140128 A2

COMPOUNDS AND COMPOSITIONS AS KINASE INHIBITORS

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. 61/052,879, filed May 13, 2008 and U.S. Provisional Patent Application No. 61/152,872, filed February 16, 2009. The disclosure of the priority applications are incorporated herein by reference in their entirety and for all purposes.

FIELD OF THE INVENTION

[0002] The invention relates to protein kinase inhibitors, and methods of using such compounds.

BACKGROUND OF THE INVENTION

[0003] Protein kinases (PK) are a large set of structurally related phosphoryl transferases having highly conserved structures and catalytic functions. Protein kinases are enzymatic components of the signal transduction pathways which catalyze the transfer of the terminal phosphate from ATP to the hydroxy group of tyrosine, serine and/or threonine residues of proteins, and are therefore categorized into families by the substrates they phosphorylate: Protein Tyrosine Kinases (PTK), and Protein Serine/Threonine Kinases.

[0004] Protein kinases play a critical role in the control of cell growth and differentiation and are responsible for the control of a wide variety of cellular signal transduction processes, wherein protein kinases are key mediators of cellular signals leading to the production of growth factors and cytokines. The overexpression or inappropriate expression of normal or mutant protein kinases plays a significant role in the development of many diseases and disorders including, central nervous system disorders such as Alzheimer's, inflammatory disorders such as arthritis, bone diseases such as osteoporosis, metabolic disorders such as diabetes, blood vessel proliferative disorders such as angiogenesis, autoimmune diseases such as rheumatoid arthritis, ocular diseases, cardiovascular disease, atherosclerosis, cancer, thrombosis, psoriasis, restenosis, schizophrenia, pain sensation, transplant rejection and infectious diseases such as viral, and fungal infections.

[0005] Examples of protein-tyrosine kinases include, but are not limited to, Irk, IGFR-1, Zap-70, Bmx, Btk, CHK (Csk homologous kinase), CSK (C-terminal Src Kinase), Itk-1, Src (c-Src, Lyn, Fyn, Lck, Syk, Hck, Yes, Blk, Fgr and Frk), Tec, Txk/Rlk, Abl, EGFR (EGFR-1/ErbB-1, ErbB-2/NEU/HER-2, ErbB-3 and ErbB-4), FAK, FGF1R (also FGFR1 or FGR-1), FGF2R (also FGR-2), MET (also Met-I or c-MET), PDGFR (α and β), Tie-1, Tie-2 (also Tek-1 or Tek), VEGFR1 (also FLT-1), VEGFR2 (also KDR), FLT-3, FLT-4, c-KIT, JAK1, JAK2, JAK3, TYK2, LOK, RET, TRKA, TRKB, TRKC, PYK2, ALK (Anaplastic Lymphoma Kinase), EPHA (1-8), EPHB (1-6), RON, Ros, Fes, Fer or EPHB4 (also EPHB4-1).

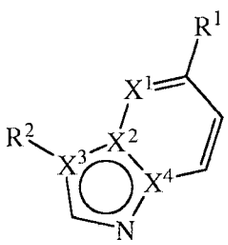
[0006] Examples of protein-serine/threonine kinases include, but are not limited to, Ark, ATM (1-3), CamK (1-IV), CamKK, Chk1 and 2 (Checkpoint kinases), CKI, CK2, Erk, IKK-I (also IKK-ALPHA or

CHUK), IKK-2 (also IKK-BETA), Ilk, Jnk (1-3), LimK (1 and 2), MLK3Raf (A, B and C), CDK (1-10), PKC (including all PKC subtypes), Plk (1-3), NIK, Pak (1-3), PDK1, PKR, RhoK, RIP, RIP-2, GSK3 (α and β), PKA, P38, Erk (1-3), PKB (including all PKB subtypes) (also AKT-1, AKT-2, AKT-3 or AKT3-1), IRAK1, FRK, SGK, TAK1 or Tp1-2 (also COT).

SUMMARY OF THE INVENTION

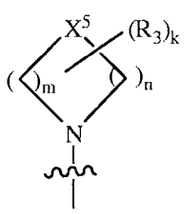
[0007] Provide herein are compounds and pharmaceutical compositions thereof, which are useful as protein kinase inhibitors.

[0008] In one aspect, the present invention provides compounds having Formula (I), 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:



Formula (I)

wherein:

R^1 is  ; wherein,

X^1, X^2, X^3 and X^4 are each independently CR^9, C or N, with the proviso that at least one of X^1, X^2 X^3 and X^4 is N and at most only two of X^1, X^2 X^3 and X^4 are N;

X^5 is $C(R^3)_2$, O, S, $S(O)_2$, S(O), or NR^3;

m is 1, 2, 3 or 4;

n is 0, 1, 2 or 3;

k is 0, 1, 2, 3, 4, 5 or 6;

each R^3 is independently selected from halogen, nitro, $-N(R^4)_2$, $-OR^9$, -CN, =O, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-C(O)OR^9$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, $-OC(O)R^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, C_1-C_8alkyl, C_6-C_{14}aryl, C_3-C_8cycloalkyl, halo-substituted-C_1-C_8alkyl, C_1-C_8alkoxy,

hydroxyl-C_1-C_8alkyl, halo-substituted C_1-C_8alkoxy, C_2-C_{14}heterocycloalkyl and C_2-C_{13}heteroaryl, wherein the C_1-C_8alkyl, C_6-C_{14}aryl, C_3-C_8cycloalkyl, C_2-C_{14}heterocycloalkyl and C_2-C_{13}heteroaryl of R^3 are optionally substituted with 1 to 3 substituents independently selected from halogen, amino, nitro, hydroxyl, cyano, $-OR^9$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-C(O)OR^9$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, $-OC(O)R^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, C_1-C_8alkyl, C_1-C_8aminoalkyl, C_1-C_8alkoxy, C_1-C_8alkylthio, hydroxyl-C_1-C_8alkyl, halo-substituted-C_1-C_8alkyl, halo-substituted-C_1-C_8alkoxy, C_3-C_8cycloalkyl, C_2-C_{14}heterocycloalkyl, C_6-C_{14}aryl and C_2-C_{13}heteroaryl;

alternatively each R^3 is independently a C_1-C_8alkyl, wherein at least two R^3 together form a C_3-C_8cycloalkyl fused with a heterocycle and wherein each C_1-C_8alkyl of R^3 is optionally substituted with 1 to 3 substituents independently selected from halogen, amino, nitro, hydroxyl, cyano, $-OR^9$, C_1-C_8alkyl, C_1-C_8aminoalkyl, C_1-C_8alkoxy, C_1-C_8alkylthio, hydroxyl-C_1-C_8alkyl, halo-substituted-C_1-C_8alkyl, halo-substituted-C_1-C_8alkoxy, C_3-C_8cycloalkyl, C_2-C_{14}heterocycloalkyl, C_6-C_{14}aryl and C_2-C_{13}heteroaryl;

R^2 is C_6-C_{14}aryl, C_2-C_{13}heteroaryl or C_2-C_{14}heterocycloalkyl, wherein the C_6-C_{14}aryl, C_2-C_{13}heteroaryl or C_2-C_{14}heterocycloalkyl of R^2 are optionally substituted with 1 to 3 substituents independently selected from halogen, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-OC(O)R^9$, C_1-C_8alkoxy, hydroxyl-C_1-C_8alkyl, halo-substituted C_1-C_8alkyl and halo-substituted C_1-C_8alkoxy;

each R^4 is independently selected from H, C_1-C_8 alkyl, $-L^1R^5$, $-L^1R^6$, $-L^1R^8$, C_2-C_{13}heteroaryl, C_6-C_{14}aryl, C_2-C_{14}heterocycloalkyl and C_3-C_8cycloalkyl, wherein the C_1-C_8alkyl, C_2-C_{13}heteroaryl and C_3-C_8cycloalkyl are optionally substituted with 1 to 3 substituents independently selected from halogen, deuterium, $-CD_3$, $-S(O)_2R^9$, -CN, C_1-C_8alkyl, $-OR^9$, $-N(R^9)_2$ and $-(CH_2)_pOR^9$;

L^1 is a bond, C_1-C_8alkylene, C_2-C_8alkenylene, $-O(CH_2)_p$-, -C(O)-, $-N(R^9)$-, $(CH_2)_pC(O)$-, $-C(O)(CH_2)_pO(CH_2)_p$- or -C(O)O-;

Y^1 is C_6-C_{14}arylene, C_2-C_{13}heteroarylene, C_3-C_8cycloalkylene, C_2-C_{14}heterocycloalkylene or C_1-C_8alkoxylene, each of which is optionally substituted with 1 to 3 substituents independently selected from halogen, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, –$C(O)N(R^4)_2$, –$N(R^4)C(O)OR^4$, –$N(R^4)C(O)R^4$, -$C(O)R^9$, -OR^9, -$C(O)OR^9$, –$N(R^4)_2$, -R^6, –OR^6, -L^1R^5, -L^1R^6, -Y^1R^5, -Y^1R^6, –$S(O)_2R^9$, –$S(O)_2N(R^4)_2$, –$NR^4S(O)_2R^4$, -$OC(O)R^9$, C_1-C_8alkoxy, hydroxyl-C_1-C_8alkyl, halo-substituted C_1-C_8alkyl and halo-substituted C_1-C_8alkoxy;

R^5 is C_6-C_{14}aryl, C_2-C_{13}heteroaryl, C_2-C_{14}heterocycloalkyl, -$N(R^9)_2$, –$N(R^9)C(O)R^9$, –$C(O)N(R^9)_2$, -$(CH_2)_pOR^9$ or -OR^9.

R^6 is C_6-C_{14}aryl, C_2-C_{13}heteroaryl, C_2-C_{14}heterocycloalkyl, -$OCH(R^7)_2$, -$C(O)R^7$, C_1-C_8alkyl, or C_3-C_8cycloalkyl, wherein the C_1-C_8alkyl, C_3-C_8cycloalkyl, C_6-C_{14}aryl, C_2-C_{13}heteroaryl, and C_2-C_{14}heterocycloalkyl of R^6 are optionally substituted with 1 to 3 substituents independently selected from halogen, –CN,–OR^9, -$(CH_2)_pOR^9$, -$L^1C(O)R^8$, -L^1R^8, -L^1R^5, -$C(O)R^9$, -$OC(O)R^9$, -$C(O)OR^9$, -$C(O)R^8$, $OC(O)N(R^4)_2$, -$N(R^9)_2$, -$C(O)C(O)OR^9$, –$(CH_2)_pN(R^9)_2$, -$N(R^4)_2$, –$C(O)N(R^4)_2$, –$N(R^4)C(O)R^4$, –$N(R^4)C(O)OR^4$, –$(CH_2)_pS(O)_2R^9$, –$S(O)_2R^9$, –$S(O)_2N(R^4)_2$, –$NR^4S(O)_2R^4$, –$NR^4S(O)_2R^9$, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_2-C_8alkene, C_1-C_8alkoxy, hydroxyl-substituted C_1-C_8alkyl, halo-substituted C_1-C_8alkyl and halo-substituted C_1-C_8alkoxy;

or R^6 is C_6-C_{14}aryl, C_2-C_{13}heteroaryl, C_2-C_{14}heterocycloalkyl or C_3-C_8cycloalkyl having a C_1-C_4alkyl bridge;

or R^6 is a C_2-C_{14}heterocycloalkyl optionally substituted with 1 to 3 substituents independently selected from halogen, =O, –CN,–OR^9, -$(CH_2)_pOR^9$, -$L^1C(O)R^8$, -L^1R^8, -L^1R^5, -$C(O)R^9$, -$OC(O)R^9$, -$C(O)OR^9$, -$C(O)R^8$, $OC(O)N(R^4)_2$, -$N(R^9)_2$, -$C(O)C(O)OR^9$, –$(CH_2)_pN(R^9)_2$, -$N(R^4)_2$, –$C(O)N(R^4)_2$, –$N(R^4)C(O)R^4$, –$N(R^4)C(O)OR^4$, –$(CH_2)_pS(O)_2R^9$, –$S(O)_2R^9$, –$S(O)_2N(R^4)_2$, –$NR^4S(O)_2R^4$, –$NR^4S(O)_2R^9$, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_2-C_8alkene, C_1-C_8alkoxy, hydroxyl-substituted C_1-C_8alkyl, halo-substituted C_1-C_8alkyl and halo-substituted C_1-C_8alkoxy;

each R^7 is independently selected from H, C_1-C_8alkyl and -L^1R^8;

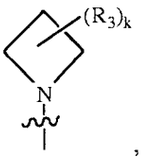
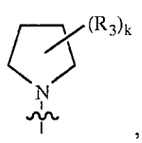
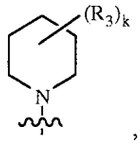
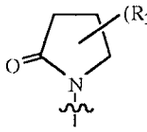
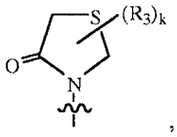
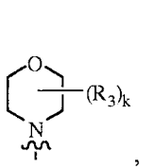
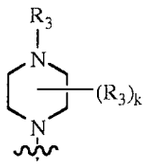
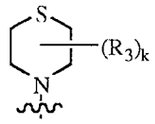
R^8 is H, -$N(R^9)_2$, -$N(R^4)_2$, -SR^9, -CN, C_1-C_8alkyl, C_3-C_8cycloalkyl and C_2-C_{14}heterocycloalkyl, wherein the C_1-C_8alkyl, C_3-C_8cycloalkyl and C_2-C_{14}heterocycloalkyl of R^8 are optionally substituted with 1 to 3 substituents independently selected from halogen, C_1-C_6alkyl, –CN,–OR^9, -$(CH_2)_pOR^9$, -

$L^1C(O)R^8$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-N(R^9)_2$, $-N(R^4)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, and $-NR^4S(O)_2$;

each R^9 is independently selected from H, C_3-C_8cycloalkyl and C_1-C_8alkyl,

and

each p is independently 1, 2, 3, 4, 5 or 6.

[0009] In certain embodiments of the aforementioned compounds of Formula (I), R^1 is  ,  ,  ,  or  , while in other embodiments R^1 is  ,  or  .

[00010] In certain embodiments of the aforementioned compounds of Formula (I), each R^3 is independently selected from halogen, $-OR^9$, C_1-C_8alkyl, C_6-C_{14}aryl, C_3-C_8cycloalkyl, halo-substituted-C_1-C_8alkyl, C_2-C_{14}heterocycloalkyl and C_2-C_{13}heteroaryl, wherein the C_1-C_8alkyl, C_6-C_{14}aryl, C_3-C_8cycloalkyl, C_2-C_{14}heterocycloalkyl and C_2-C_{13}heteroaryl of R^3 are optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxyl, $-OR^9$, C_1-C_8alkyl, C_1-C_8alkoxy, hydroxyl-C_1-C_8alkyl, halo-substituted-C_1-C_8alkyl, halo-substituted-C_1-C_8alkoxy and C_3-C_8cycloalkyl.

[00011] In certain embodiments of the aforementioned compounds of Formula (I), the C_6-C_{14}aryl of R^3 is phenyl optionally substituted with 1 to 3 substituents independently selected from halogen, C_1-C_8alkyl, and halo-substituted-C_1-C_8alkyl.

[00012] In certain embodiments of the aforementioned compounds of Formula (I), the C_6-C_{14}aryl of R^3 is phenyl optionally substituted with 1 to 3 substituents independently selected from fluoro and C_1-C_8alkyl.

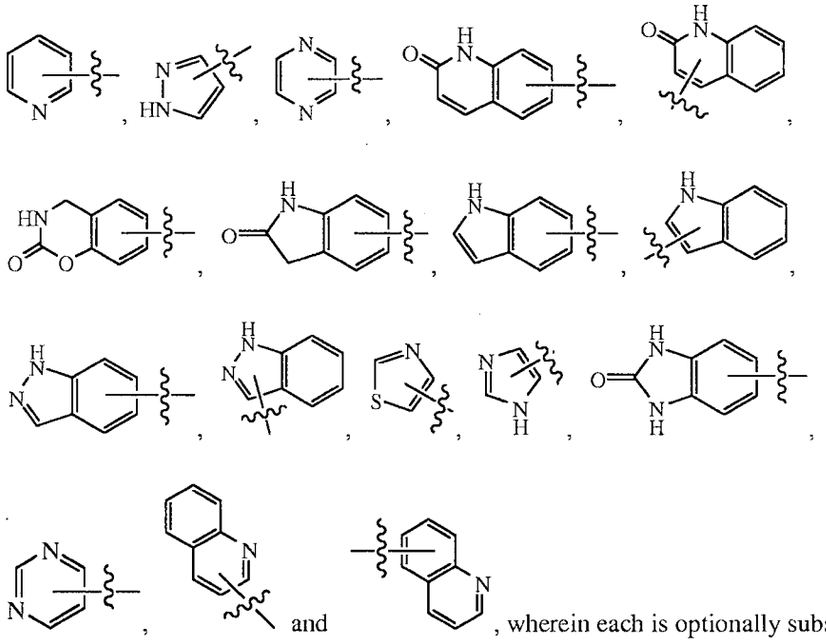
[00013] In certain embodiments of the aforementioned compounds of Formula (I), R^2 is C_6-C_{14}aryl or C_2-C_{13}heteroaryl, wherein the C_6-C_{14}aryl and C_2-C_{13}heteroaryl of R^2 are optionally substituted with 1 to 3 substituents independently selected from halogen, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-OC(O)R^9$, C_1-C_8alkoxy, hydroxyl-C_1-C_8alkyl, halo-substituted C_1-C_8alkyl and halo-substituted C_1-C_8alkoxy.

[00014] In certain embodiments of the aforementioned compounds of Formula (I), R^2 is C_6-C_{14}aryl or C_2-C_{13}heteroaryl, wherein the C_6-C_{14}aryl and C_2-C_{13}heteroaryl of R^2 are optionally substituted with 1 to 3

substituents independently selected from halogen, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ and $-S(O)_2R^9$.

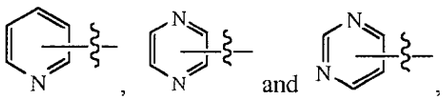
[00015] In certain embodiments of the aforementioned compounds of Formula (I), the C_6-C_{14}aryl of R^2 is phenyl optionally substituted with 1 to 3 substituents independently selected from halogen, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ and $-S(O)_2R^9$.

[00016] In certain embodiments of the aforementioned compounds of Formula (I), the C_2-C_{13}heteroaryl of R^2 is selected from



and , wherein each is optionally substituted with 1 to 3 substituents independently selected from halogen, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ and $-S(O)_2R^9$.

[00017] In certain embodiments of the aforementioned compounds of Formula (I), the C_2-C_{13}heteroaryl of R^2 is selected from

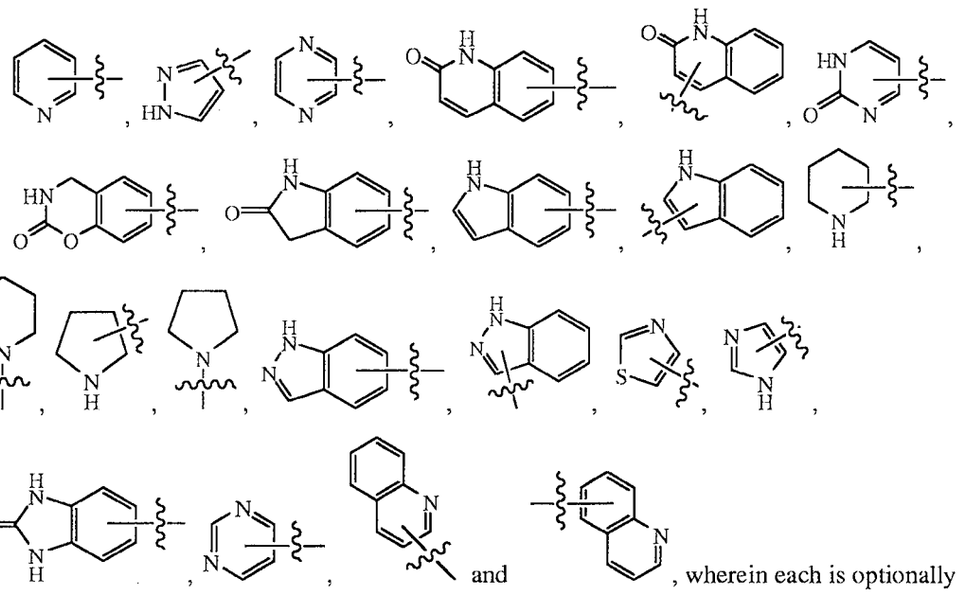


and , wherein each is optionally substituted with 1 to 3 substituents independently selected from halogen, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ and $-S(O)_2R^9$.

[00018] In certain embodiments of the aforementioned compounds of Formula (I), R^6 is C_2-

C_{13}heteroaryl, C_2-C_{14}heterocycloalkyl, -$OCH(R^7)_2$, C_1-C_8alkyl, or C_3-C_8cycloalkyl, wherein the C_1-C_8alkyl, C_3-C_8cycloalkyl, C_2-C_{13}heteroaryl, and C_2-C_{14}heterocycloalkyl of R^6 are optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, $–OR^9$, -$(CH_2)_pOR^9$, -$L^1C(O)R^8$, -L^1R^8, -L^1R^5, -$C(O)OR^9$, -$C(O)R^9$, -$N(R^9)_2$, $–C(O)N(R^4)_2$, $–N(R^4)C(O)OR^4$, $–N(R^4)C(O)R^4$, -$N(R^4)_2$, $–S(O)_2R^9$, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_2-C_8alkene, and hydroxyl-substituted C_1-C_8alkyl.

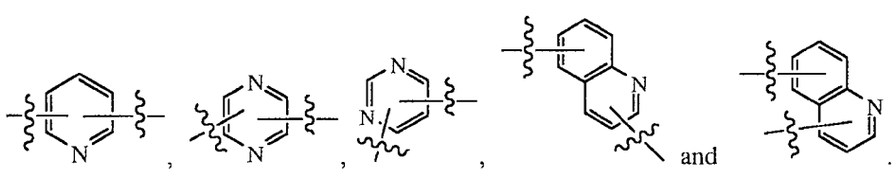
[00019] In certain embodiments of the aforementioned compounds of Formula (I), R^6 is selected from



and

, wherein each is optionally substituted with 1 to 3 substituents independently selected from halogen, –CN, $–OR^9$, -$(CH_2)_pOR^9$, -$L^1C(O)R^8$, -L^1R^8, -L^1R^5, -$C(O)OR^9$, -$C(O)R^9$, -$N(R^9)_2$, $–C(O)N(R^4)_2$, $–N(R^4)C(O)OR^4$, $–N(R^4)C(O)R^4$, -$N(R^4)_2$, $–S(O)_2R^9$, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_2-C_8alkene, and hydroxyl-substituted C_1-C_8alkyl.

[00020] In certain embodiments of the aforementioned compounds of Formula (I), Y^1 is C_6-C_{14}arylene or C_2-C_{13}heteroarylene , while in other embodiments Y^1 is selected from



and

.

[00021] In certain embodiments of the aforementioned compounds of Formula (I), each R^4 is independently selected from H, C_1-C_8 alkyl, C_6-C_{14}aryl , C_2-C_{14}heterocycloalkyl, -L^1R^5, -L^1R^6 and C_3-C_8cycloalkyl, wherein the C_1-C_8alkyl, C_6-C_{14}aryl , C_2-C_{14}heterocycloalkyl, and C_3-C_8cycloalkyl are optionally substituted with -$(CH_2)_pOR^9$.

[00022] In certain embodiments of the aforementioned compounds of Formula (I), R^5 is C_6-C_{14}aryl, C_2-C_{13}heteroaryl, C_2-C_{14}heterocycloalkyl, -$N(R^9)_2$, $–N(R^9)C(O)R^9$, -$(CH_2)_pOR^9$, or -OR^9.

[00023] In certain embodiments of the aforementioned compounds of Formula (I), R^7 is $-L^1R^8$. In certain embodiments of the aforementioned compounds of Formula (I), R^8 is $-N(R^9)_2$ or –CN.

[00024] In certain embodiments compounds of Formula (I) are selected from:

(R)-1-(4-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)pyrrolidin-3-ol; (R)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)piperidin-4-ol; 6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)indolin-2-one; 3-(6-((3S)-2-(3-fluorophenyl)-3-hydroxypyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 5-(6-(2-(2,5-dimethylphenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-fluorobenzonitrile; (R)-4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 4-(5-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)morpholine; 4-(5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)morpholine; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-N-methylpicolinamide; 4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 5-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-N-methylpicolinamide; (S)-4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; (R)-4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 4-(5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)morpholine; 4-(6-(2-phenylazetidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; (R)-4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; (S)-4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 4-(6-(2-(3-fluorophenyl)-2-methylpyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one; 6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)indolin-2-one; 6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)indolin-2-one; 4-(6-(2-(2,5-difluorophenyl)-5-methylpyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 4-(2-(4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1H-pyrazol-1-yl)ethyl)morpholine; N-(2-(4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1H-pyrazol-1-yl)ethyl)acetamide; (Z)-3-((1H-pyrrol-2-yl)methylene)-6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)indolin-2-one; 5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-fluorobenzonitrile; 5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-morpholinobenzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-fluorobenzonitrile; 5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(dimethylamino)benzonitrile; 5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-methylpiperazin-1-yl)benzonitrile; 5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-(2-methoxyethyl)piperazin-1-yl)benzonitrile; 5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-morpholinoethylamino)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(dimethylamino)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-methylpiperazin-1-yl)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-(2-methoxyethyl)piperazin-1-yl)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-morpholinoethylamino)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-morpholinobenzonitrile; 3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-morpholinopiperidin-1-yl)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(pyrrolidin-1-yl)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(3-(dimethylamino)pyrrolidin-1-yl)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2,6-dimethylmorpholino)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-(pyrrolidin-1-yl)ethoxy)benzonitrile; 5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)nicotinonitrile; 6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinonitrile; 4-(4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)thiazol-2-

yl)morpholine; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(3-morpholinopropylamino)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(3-morpholinopyrrolidin-1-yl)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(1-methylpyrrolidin-3-yloxy)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-((2-(dimethylamino)ethyl)(methyl)amino)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-((1-methylpyrrolidin-3-yl)methoxy)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(3-morpholinopropoxy)benzonitrile; 3-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile; 4-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile; 3-(5-(2-(2,5-difluorophenyl)thiazolidin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile; 3-(5-(2-(2,5-difluorophenyl)thiazolidin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile; 3-(3-(1H-imidazol-2-yl)phenyl)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3H-imidazo[4,5-b]pyridine; 3-(5-(2-(2,5-difluorophenyl)-4-oxothiazolidin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile; 3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile; 4-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile; 3-(6-(2-(3-fluorophenyl)-3-oxopyrazolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 5-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)-2-(4-hydroxypiperidin-1-yl)benzonitrile; 2-(1,3-bis(dimethylamino)propan-2-yloxy)-4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(1-(dimethylamino)propan-2-yloxy)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-(1-methylpyrrolidin-2-yl)ethoxy)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(3-(dimethylamino)-2-hydroxypropoxy)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)benzonitrile; 4-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 3-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 2-(2-(diethylamino)ethylamino)-4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 7-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-oxo-1,2-dihydroquinoline-3-carbonitrile; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-morpholinobenzonitrile; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-methylpiperazin-1-yl)benzonitrile; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-(2-methoxyethyl)piperazin-1-yl)benzonitrile; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-morpholinoethylamino)benzonitrile; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-morpholinopiperidin-1-yl)benzonitrile; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-(pyrrolidin-1-yl)ethoxy)benzonitrile; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-(1-methylpyrrolidin-2-yl)ethoxy)benzonitrile; 4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-methylpiperazin-1-yl)benzonitrile; 4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-(pyrrolidin-1-yl)ethoxy)benzonitrile; 4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-morpholinoethoxy)benzonitrile; (R)-3-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; (S)-3-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 4-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; (R)-4-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; (S)-4-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 6-(6-(2-(2,5-dimethylphenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinic acid; 3-(6-((2R,4S)-3,3-difluoro-4-methyl-2-phenylpyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 3-(6-(2-phenylpyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 6-(6-(2-phenylpyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-((R)-pyrrolidin-2-ylmethoxy)benzonitrile; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-((S)-pyrrolidin-2-ylmethoxy)benzonitrile; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-(2-morpholino-2-oxoethyl)piperazin-1-yl)benzonitrile; 2-(4-(2-cyano-4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)phenyl)piperazin-1-yl)-N,N-dimethylacetamide; 2-(4-(3-(dimethylamino)propyl)piperazin-1-yl)-5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-hydroxypiperidin-1-yl)benzonitrile; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-(4-

isopropylpiperazin-1-yl)ethoxy)benzonitrile; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-(4-(2-hydroxyethyl)piperazin-1-yl)ethoxy)benzonitrile; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(((R)-5-oxopyrrolidin-2-yl)methoxy)benzonitrile; 3-(6-((2R,4S)-3,3-difluoro-2-(3-fluorophenyl)-4-methylpyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(1H-indol-4-yl)imidazo[1,2-b]pyridazine; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(1-methyl-1H-indol-2-yl)imidazo[1,2-b]pyridazine; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(1H-indol-5-yl)imidazo[1,2-b]pyridazine; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(5-(4-methylpiperazin-1-yl)pyrazin-2-yl)imidazo[1,2-b]pyridazine; 4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(piperidin-1-yl)thiazole; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(5-(pyrrolidin-1-yl)pyrazin-2-yl)imidazo[1,2-b]pyridazine; tert-butyl 4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazine-1-carboxylate; 3-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; tert-butyl 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-methylphenylcarbamate; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(pyridin-2-yl)imidazo[1,2-b]pyridazine; 3-(6-chloropyrazin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine; 3-(6-(1H-imidazol-1-yl)pyrazin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine; 2-chloro-5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)thiazole; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-N,N-dimethylpyrazin-2-amine; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(piperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine; 4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)morpholine; (S)-6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinonitrile; (R)-6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinonitrile; 3-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)indolin-2-one; 6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(1H-indol-4-yl)imidazo[1,2-b]pyridazine; 4-(6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)morpholine; 6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(1H-indol-5-yl)imidazo[1,2-b]pyridazine; (R)-4-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; (S)-4-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(1H-indazol-5-yl)imidazo[1,2-b]pyridazine; 3-(5-fluoro-6-methylpyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine; 3-(3-fluorophenyl)-4-(3-(pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine; 6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)nicotinonitrile; 2-fluoro-5-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-methoxypyridin-2-yl)imidazo[1,2-b]pyridazine; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-fluoropyridin-2-yl)imidazo[1,2-b]pyridazine; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-N-(2-hydroxyethyl)picolinamide; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinamide; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(1H-indazol-6-yl)imidazo[1,2-b]pyridazine; 6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(1H-indazol-6-yl)imidazo[1,2-b]pyridazine; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(piperazin-1-yl)pyridin-3-yl)imidazo[1,2-b]pyridazine; 2-(4-(2-cyano-4-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)phenyl)piperazin-1-yl)-N,N-dimethylacetamide; 2-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-ylamino)ethanol; 1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol; 6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(6-fluoropyridin-2-yl)imidazo[1,2-b]pyridazine; 4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-2-one; 7-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-oxo-1,2-dihydroquinoline-3-carbonitrile; 4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(piperazin-1-ylmethyl)benzonitrile; N1,N1-diethyl-N2-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)ethane-1,2-diamine; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(4-methylpiperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine; (2S)-3-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-ylamino)propane-1,2-diol; 6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(6-(piperazin-1-yl)pyridin-3-yl)imidazo[1,2-b]pyridazine; 6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(6-(piperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine; 6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(6-(4-methylpiperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine; 4-(6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-2-one; (3S)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrrolidin-3-ol; (3R)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-

yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrrolidin-3-ol; (3S,4S)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrrolidine-3,4-diol; 3-(3-fluorophenyl)-4-(3-(5-(morpholinomethyl)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine; 4-((6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-3-yl)methyl)morpholine; 4-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)-2-((4-methylpiperazin-1-yl)methyl)benzonitrile; 1-(6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol; 3-(3-fluorophenyl)-4-(3-(6-fluoropyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine; (5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)(4-hydroxypiperidin-1-yl)methanone; 3-(3-fluorophenyl)-4-(3-(6-morpholinopyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine; 3-(3-fluorophenyl)-4-(3-(6-(piperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine; 4-(6-(2-(2-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 3-(6-(2-(2-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 4-(4-(6-(2-(2-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)thiazol-2-yl)morpholine; 5-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)-2-(4-methylpiperazin-1-yl)benzonitrile; 2-(4-acetylpiperazin-1-yl)-5-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)benzonitrile; 5-(6-(2-(2-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-hydroxypiperidin-1-yl)benzonitrile; 1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol; N-(5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyrazin-2-yl)cyclopropanecarboxamide; 4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-((4-methylpiperazin-1-yl)methyl)benzonitrile; (2S)-4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-2-methylmorpholine; 1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carboxylic acid; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-methoxythiazole; 4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)thiazole-2-carboxylic acid; (4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)thiazol-2-yl)methanol; 1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-3-ol; (3R)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N,N-dimethylpyrrolidin-3-amine; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(1-methyl-1H-imidazol-2-yl)imidazo[1,2-b]pyridazine; 5-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)-2-(piperazin-1-yl)benzonitrile; tert-butyl 4-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazine-1-carboxylate; 3-(3-fluorophenyl)-4-(3-(6-(4-methylpiperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine; 4-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-2,6-dimethylmorpholine; 3-(3-fluorophenyl)-4-(3-(6-(piperidin-4-yloxy)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine; 4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(piperazin-1-ylmethyl)thiazole; 2,2'-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-ylazanediyl)diethanol; 4-(2-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yloxy)ethyl)morpholine; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)imidazo[1,2-b]pyridazine; 4-((6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)methyl)morpholine; 4-((6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)methyl)-2,6-dimethylmorpholine; 1-((6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)methyl)pyrrolidin-3-ol; 4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-methoxythiazole; ethyl 4-(5-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-1-carboxylate; 6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)nicotinonitrile; 5-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)-1-(piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one; 2-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)-N,N-dimethylacetamide; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(4-isopropylpiperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine; 2-(1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-yl)propan-2-ol; 4-(1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-yl)morpholine; 3-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)propanenitrile; 1-(6-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol; 2-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)-N-isopropylacetamide; (1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-yl)methanol; (1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-

1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-3-yl)methanol; 1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carbonitrile; 2-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)ethanol; (6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)methanol; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(5-methyl-1H-imidazol-2-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine; 6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinamide; (R)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-fluoropyridin-2-yl)imidazo[1,2-b]pyridazine; (R)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol; (1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-yl)methanol; 2-(1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-yl)ethanol; 1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-3-carboxamide; 1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carboxamide; 6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-ol; 6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinic acid; 2-fluoro-3-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)quinoline; 3-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)quinolin-2(1H)-one; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)quinoline; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(4-(methylsulfonyl)phenyl)imidazo[1,2-b]pyridazine; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(piperidin-4-yloxy)pyridin-2-yl)imidazo[1,2-b]pyridazine; (1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-ylamino)cyclopentyl)methanol; 3-(3-fluorophenyl)-4-(3-(6-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine; 3-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)quinoline; (6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)(4-hydroxypiperidin-1-yl)methanone; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(2-fluoropyridin-4-yl)imidazo[1,2-b]pyridazine; 1-(4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol; N1,N1-diethyl-N2-(6-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)ethane-1,2-diamine; 6-(2-(3-fluorophenyl)piperidin-1-yl)-3-(6-(4-isopropylpiperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine; (3S)-1-(6-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N,N-dimethylpyrrolidin-3-amine; 4-(3-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)-3-(3-fluorophenyl)morpholine; 6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)-N-(2-(piperazin-1-yl)ethyl)pyridin-2-amine; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(1-(methylsulfonyl)piperidin-4-yloxy)pyridin-2-yl)imidazo[1,2-b]pyridazine; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-a]pyridin-3-yl)-2-fluorobenzonitrile; 2-ethoxy-4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-a]pyridin-3-yl)thiazole; 5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-a]pyridin-3-yl)-2-fluorobenzonitrile; 4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinic acid; 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinic acid; (2S,6R)-4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-2,6-dimethylmorpholine; 4-(6-(6-(2-(pyridin-2-yl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)morpholine; 1-(6-(6-(2-(pyridin-2-yl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol; 1-(6-(6-(2-(pyridin-3-yl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol; 6-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-N-methylpyridin-2-amine; 6-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-N-isopropylpyridin-2-amine; N-(6-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)methanesulfonamide; 6-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-N,N-dimethylpyridin-2-amine; 6-(2-(3-fluorophenyl)piperidin-1-yl)-3-(6-(piperidin-4-yloxy)pyridin-2-yl)imidazo[1,2-b]pyridazine; 1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)azetidine-3-carboxylic acid; 1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)azetidin-3-ol; 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-a]pyridin-3-yl)-2-ethoxythiazole; 1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol; (6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)methanol; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(5-methyl-1H-imidazol-2-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine; (1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-yl)methanol; 2-(4-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)ethanol; 1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-3-carboxamide; 1-(6-

(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carboxamide; 3-(3-fluorophenyl)-4-(3-(6-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine; 4-(3-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)-3-(3-fluorophenyl)morpholine; 6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)-N-(2-(piperazin-1-yl)ethyl)pyridin-2-amine; 1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N-methylpiperidine-4-carboxamide; 1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N-(2-hydroxyethyl)piperidine-4-carboxamide; (S)-6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)indolin-2-one; (R)-6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)indolin-2-one; (S)-1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol; (R)-1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol; ethyl 1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carboxylate; 3-(6-(1,3-dioxolan-2-yl)pyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine; 1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carboxylic acid; 5-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)oxazole; 3-(3-fluorophenyl)-4-(3-(6-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine; N-(cyclopropylmethoxy)-1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carboxamide; 1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N-isopropylpiperidine-4-carboxamide; N-cyclopropyl-1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carboxamide; 1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N-(isoxazol-3-yl)piperidine-4-carboxamide; (1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-yl)(3-hydroxypyrrolidin-1-yl)methanone; N-(cyanomethyl)-1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carboxamide; 2-(1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-yl)ethanol; 3-(6-(1H-pyrazol-5-yl)pyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine; 5-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carbonitrile; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(2-methylpyrimidin-4-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine; 4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-amine; 3-(6-((2R,5S)-2,5-dimethylpiperazin-1-yl)pyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine; 3-(6-((3S,5R)-3,5-dimethylpiperazin-1-yl)pyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine; 6-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2(1H)-one; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(4-(pyrazin-2-yl)piperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine; 4-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)morpholine; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine; 2-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-ylamino)ethanol; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(6-(piperidin-4-yl)pyrimidin-4-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine; 2-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)-N,N-dimethylethanamine; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(pyrimidin-4-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine; 4-(1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrrolidin-3-yl)morpholine; 3-(6-(4-(cyclopropylsulfonyl)piperazin-1-yl)pyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine; 1-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)-2-hydroxyethanone; (4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)(1-hydroxycyclopropyl)methanone; (R)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(2-methylpyrimidin-4-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine; (4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone; (4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)(tetrahydrofuran-2-yl)methanone; 4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,3'-bipyridin-6'-

yl)morpholine; 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(5-(pyrrolidin-1-yl)pyrazin-2-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine; 4-(5-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)morpholine; 1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)piperidin-4-ol; N1-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)-N2,N2-dimethylethane-1,2-diamine; 1-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)piperidin-4-ol; 4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N,N-dimethylpyrimidin-2-amine; 3-(6-(1H-indazol-5-yl)pyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine; 2-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,3'-bipyridin-6'-ylamino)ethanol; 1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,3'-bipyridin-6'-yl)piperidin-4-ol; (R)-2-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-ylamino)ethanol; 4-((S)-1-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrrolidin-3-yl)morpholine; (2S,6R)-4-((S)-1-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrrolidin-3-yl)-2,6-dimethylmorpholine; (R)-1-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)azetidin-3-ol; (R)-N-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)methanesulfonamide; (R)-4-((S)-1-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrrolidin-3-yl)-2-methylmorpholine; (R)-2-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-ylamino)ethanol; (R)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)azetidin-3-ol; (R)-1-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)pyrrolidin-3-ol; (R)-N-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)methanesulfonamide; (R)-4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N-(pyridin-3-ylmethyl)pyrimidin-2-amine; (S)-1-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)-N-methylpyrrolidin-3-amine; (R)-4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N-(2-(methylsulfonyl)ethyl)pyrimidin-2-amine; (R)-N-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,3'-bipyridin-6'-yl)methanesulfonamide; (R)-3-(6-(1H-indazol-6-yl)pyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine; (R)-1-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)-N-methylpyrrolidin-3-amine; (R)-1-(6'-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,2'-bipyridin-6-yl)piperidin-4-ol; (R)-2-(6'-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,2'-bipyridin-6-ylamino)ethanol; (R)-1-(6'-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,2'-bipyridin-6-yl)-N-methylpyrrolidin-3-amine; (R)-1-(4-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)-N-methylpyrrolidin-3-amine; (R)-2-(4-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)piperazin-1-yl)ethanol; (R)-2-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)piperazin-1-yl)ethanol; 1-((2S,6R)-4-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-2,6-dimethylpiperazin-1-yl)-2-hydroxyethanone; (R)-1-(6'-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,2'-bipyridin-6-yl)pyrrolidin-3-ol; (R)-2-(4-(6'-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,2'-bipyridin-6-yl)piperazin-1-yl)ethanol; (R)-4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)benzenesulfonamide; (R)-3-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)benzenesulfonamide; (R)-N-(6'-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,2'-bipyridin-6-yl)methanesulfonamide; (R)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(2'-(piperazin-1-yl)-2,4'-bipyridin-6-yl)imidazo[1,2-b]pyridazine; (R)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(4-(methylsulfonyl)phenyl)pyridin-2-yl)imidazo[1,2-b]pyridazine; (R)-4-(2-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-1H-pyrazol-1-yl)ethyl)morpholine; (R)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(2'-(4-isopropylpiperazin-1-yl)-2,4'-bipyridin-6-yl)imidazo[1,2-b]pyridazine; (R)-4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N-methylbenzenesulfonamide; (S)-1-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)pyrrolidin-3-ol; 2-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-(piperidin-4-yloxy)pyridine; {1-[(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)amino]cyclopentyl}methanol;

(3S,4S)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidine-3,4-diol; 1-{6-[6-(3-phenylthiomorpholin-4-yl)imidazo[1,2-b]pyridazin-3-yl]pyridin-2-yl}piperidin-4-ol; 2-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-[(1-methanesulfonylpiperidin-4-yl)oxy]pyridine; (3S,4S)-1-(6-{6-[(2S)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidine-3,4-diol; (3S,4S)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidine-3,4-diol; 4-(4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-1H-pyrazol-1-yl)piperidine; N-[(3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-N-methylmethanesulfonamide; 2-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-(3-fluoropiperidin-1-yl)pyridine; N-[(3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-N-methylacetamide; N-[(3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-2-hydroxy-N-methylacetamide; 2-(3,3-difluoropiperidin-1-yl)-6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine; N-ethyl-N-[(3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]acetamide; N-ethyl-N-[(3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-2-hydroxyacetamide; N-[(3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]methanesulfonamide; N-[1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl]-N-methylmethanesulfonamide; N-[1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl]acetamide; 1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-3-methylpiperidin-4-ol; 1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-amine; 2,2,2-trifluoro-N-[(3S)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]acetamide; N-[(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]methanesulfonamide; N-ethyl-N-[(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]acetamide; N-[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-yl]-N-methylmethanesulfonamide; (3S)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-amine; 2-(dimethylamino)-1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]ethan-1-one; (3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-3-methylpiperazine; 2-[(2R)-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-2-methylpiperazin-1-yl]-2-oxoethyl acetate; 1-[(2R)-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-2-methylpiperazin-1-yl]-2-hydroxyethan-1-one; 2-amino-1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]ethan-1-one; 1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-2-(methylamino)ethan-1-one; 2-(dimethylamino)-1-[(2R)-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-2-methylpiperazin-1-yl]ethan-1-one; (3R)-3-{[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]carbonyl}morpholine; (3R)-3-{[(2R)-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-2-methylpiperazin-1-yl]carbonyl}morpholine; 8-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-octahydropiperazino[2,1-c]morpholin-4-one; (3R,4R)-1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyridin-2-yl]pyrrolidine-3,4-diol; 1-(6-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-ol; 6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine-2-carboxamide; 6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-ol; 6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine-2-carboxylic acid; 2-fluoro-3-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}quinoline; 3-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-1,2-dihydroquinolin-2-one; 5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}quinoline; 2-(3-fluorophenyl)-1-[3-(4-methanesulfonylphenyl)imidazo[1,2-b]pyridazin-6-yl]pyrrolidine; 3-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}quinoline; 1-[(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)carbonyl]piperidin-4-ol; 2-fluoro-4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine; 1-(4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-

b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-ol; 1-(4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-methylpiperazine; 2-[(4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)amino]ethan-1-ol; (3R)-1-[(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)carbonyl]-N,N-dimethylpyrrolidin-3-amine; 1-(5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrimidin-2-yl)piperidin-4-ol; 6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-N-methylpyridine-2-carboxamide; 4-[(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)carbonyl]morpholine; (3R)-1-(4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-ol; (3S)-1-(4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-ol; (3R,4R)-1-(4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidine-3,4-diol; 1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N,N-dimethylpiperidin-4-amine; 2-[(5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrimidin-2-yl)amino]ethan-1-ol; 5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-N-methylpyrimidin-2-amine; 5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-N,N-dimethylpyrimidin-2-amine; 1-(4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N,N-dimethylpiperidin-4-amine; 2-chloro-5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrimidine; tert-butyl 4-[(5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrimidin-2-yl)oxy]piperidine-1-carboxylate; 5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-2-(piperidin-4-yloxy)pyrimidine; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N,N-dimethylpiperidin-4-amine; 5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrimidine; 5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-1,2-dihydropyrimidine; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-one; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazine; 6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-N-[1-(propan-2-yl)piperidin-4-yl]pyridin-2-amine; [1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl] carbamate; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl N-methylcarbamate; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl N-tert-butylcarbamate; 1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]ethan-1-one; N,N-diethyl-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-amine; 2,2,2-trifluoro-1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]ethan-1-one; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-methanesulfonylpiperazine; 2-(benzyloxy)-1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]ethan-1-one; 1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-2-hydroxyethan-1-one; 2-{[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl]amino}ethan-1-ol; 2-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-(1,2,3,6-tetrahydropyridin-1-yl)pyridine; N,N-diethyl-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-amine; N-cyclopropyl-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-amine; (3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-methylpyrrolidin-3-amine; (3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-methylpyrrolidin-3-amine; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-methylpiperidin-4-amine; 2-fluoro-N-[1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-N,2-dimethylpropanamide; 2-fluoro-N-[1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-N-methylpropanamide; 1-tert-butyl-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazine; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidine-3-carboxylic acid; 2-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-[4-(pyrrolidin-1-yl)piperidin-1-yl]pyridine; 2-fluoro-N-[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl]-N,2-dimethylpropanamide; 2,2,2-trifluoro-N-[(3R)-1-(6-{6-[(2R)-2-(3-

fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-N-methylacetamide; 6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-N-methyl-N-(piperidin-4-yl)pyridin-2-amine; 2-fluoro-N-[(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-N,2-dimethylpropanamide; [1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-yl]methanol; (3R)-N-(2-fluoro-2-methylpropyl)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-methylpyrrolidin-3-amine; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-(propane-2-sulfonyl)piperazine; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-[(2-methylpropane)sulfonyl]piperazine; 1-(butane-2-sulfonyl)-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazine; 1-(ethanesulfonyl)-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazine; (3S)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-methylpyrrolidin-3-amine; (3S)-N-ethyl-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-amine; (3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-(2,2,2-trifluoroethyl)pyrrolidin-3-amine; 2-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-2-oxoethyl acetate; {[(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]carbamoyl}methyl acetate; N-[(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-2-hydroxyacetamide; 4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-1-methylpiperazin-2-one; 4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-1-(2-hydroxyethyl)piperazin-2-one; 2-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-[4-(piperidin-1-yl)piperidin-1-yl]pyridine; {[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl]methyl}dimethylamine; 2-(4,4-dimethylpiperidin-1-yl)-6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine; 2-(3,3-dimethylpiperidin-1-yl)-6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine; 4-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]benzoic acid; 1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-2-methyl-1-oxopropan-2-yl acetate; (2S)-1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-1-oxopropan-2-yl acetate; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N,N-dimethylpiperidin-4-amine; N,N-diethyl-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazine-1-sulfonamide; N-ethyl-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-methylpiperidin-4-amine; (2S)-1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-2-hydroxypropan-1-one; 1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-2-hydroxy-2-methylpropan-1-one; 8-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane; 4-ethyl-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-ol; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-(propan-2-yl)piperidin-4-ol; 4-ethenyl-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-ol; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-methylpiperidin-4-ol; 2-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-{octahydropyrrolo[1,2-b]piperazin-2-yl}pyridine; 8-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-3-methyl-1,3,8-triazaspiro[4.5]decane-2,4-dione; (1S)-1-{[(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]carbamoyl}ethyl acetate; (2S)-N-[(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-2-hydroxypropanamide; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-3-(trifluoromethyl)piperazine; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-methylpiperidin-3-amine; 1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyridin-2-yl]-N,N-dimethylpiperidin-4-amine; 2-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-

18

b]pyridazin-3-yl}pyridin-2-yl)-2-(trifluoromethyl)piperazin-1-yl]-2-oxoethyl acetate; 1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-2-(trifluoromethyl)piperazin-1-yl]-2-hydroxyethan-1-one; 1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyridin-2-yl]-N-methylpiperidin-4-amine; 4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyridin-2-ol; N-cyclobutyl-6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-amine; N-cyclopropyl-6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-amine; N-cyclopropyl-1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyridin-2-yl]piperidin-4-amine; 1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyridin-2-yl]piperidin-4-one; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-(pyridin-3-yl)piperazine; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-(pyridin-2-yl)piperazine; 1-(4-fluorophenyl)-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazine; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-(6-methylpyridin-2-yl)piperazine; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine; 2-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-N-methyl-N-phenylacetamide; 2-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-2-oxoacetic acid; 6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine-2-carboxamide; 6-{6-[(2S)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine-2-carboxamide; 2-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]ethan-1-ol; 2-[4-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-N-(propan-2-yl)acetamide; [1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl]methanol; [1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-3-yl]methanol; 1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidine-4-carbonitrile; 2-[4-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]ethan-1-ol; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-ol; 2-fluoro-6-{6-[(2S)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine; 2-fluoro-6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine; diethyl({2-[(6-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)amino]ethyl})amine; 1-(6-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-(propan-2-yl)piperazine; (3S)-1-(6-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N,N-dimethylpyrrolidin-3-amine; 6-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-N-methylpyridin-2-amine; 6-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-N-(propan-2-yl)pyridin-2-amine; N-(6-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)methanesulfonamide; 6-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-N,N-dimethylpyridin-2-amine; 2-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-(piperidin-4-yloxy)pyridine; 1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-ol; (3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N,N-dimethylpyrrolidin-3-amine; 1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-(2-hydroxyethyl)piperidine-4-carboxamide; N-[2-(dimethylamino)ethyl]-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidine-4-carboxamide; 1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidine-3-carboxylic acid; N-(cyanomethyl)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidine-4-carboxamide; 2-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrazine; N-[(3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]acetamide; 1-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-1H-pyrazole; 1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrazin-2-yl)piperidin-4-ol; (3S)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrazin-2-yl)-N,N-dimethylpyrrolidin-3-amine; 2-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-(piperazin-1-yl)pyrazine; 2-[4-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrazin-2-yl)piperazin-1-yl]ethan-1-ol; (3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrazin-2-yl)-N,N-

dimethylpyrrolidin-3-amine; N-[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-yl]acetamide; 1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-amine; N-[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-yl]methanesulfonamide; N-ethyl-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-amine; N,N-diethyl-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-amine; 3-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-1H-pyrrole; N-[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-yl]-2-hydroxyacetamide; N-ethyl-N-[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-yl]methanesulfonamide; 1-[6-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyridin-2-yl]piperidin-4-ol; 6-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-2-oxa-6-azaspiro[3.3]heptane; 6-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrimidin-2-yl]-2-oxa-6-azaspiro[3.3]heptane; 6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-2,3-dihydro-1H-indol-2-one; 6-{6-[3-(3-fluorophenyl)morpholin-4-yl]imidazo[1,2-b]pyridazin-3-yl}-2,3-dihydro-1H-indol-2-one; 3-(3-fluorophenyl)-4-{3-[6-(piperazin-1-yl)pyridin-2-yl]imidazo[1,2-b]pyridazin-6-yl}morpholine; (3S)-4-[3-(6-fluoropyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl]-3-phenylmorpholine; 1-(6-{6-[(3S)-3-phenylmorpholin-4-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-ol; 1-(6-{6-[3-(3-fluorophenyl)morpholin-4-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidine-4-carbaldehyde; 3-(3-fluorophenyl)-4-(3-{6-[4-(4-methyl-1H-imidazol-2-yl)piperidin-1-yl]pyridin-2-yl}imidazo[1,2-b]pyridazin-6-yl)morpholine; 6-{6-[3-(3-fluorophenyl)morpholin-4-yl]imidazo[1,2-b]pyridazin-3-yl}-N,N-dimethylpyridin-2-amine; 3-(3-fluorophenyl)-4-[3-(6-{4-[2-(methylsulfanyl)ethyl]piperazin-1-yl}pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl]morpholine; 3-(3-fluorophenyl)-4-(3-{6-[4-(2-methanesulfonylethyl)piperazin-1-yl]pyridin-2-yl}imidazo[1,2-b]pyridazin-6-yl)morpholine; (N-cyclopropyl-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)piperidin-4-amine); 3-(3-fluorophenyl)-4-(3-{6-[4-(1H-1,2,4-triazol-5-yl)piperidin-1-yl]pyridin-2-yl}imidazo[1,2-b]pyridazin-6-yl)morpholine, and 3-(3-fluorophenyl)-4-(3-{6-[4-(1,2,4-oxadiazol-5-yl)piperidin-1-yl]pyridin-2-yl}imidazo[1,2-b]pyridazin-6-yl)morpholine.

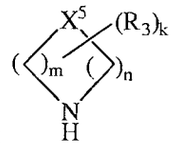
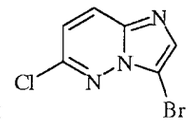
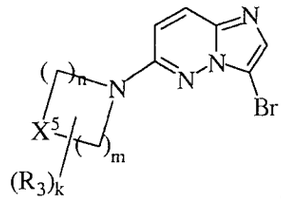
[00025] Another aspect provided herein are pharmaceutical compositions comprising a therapeutically effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier.

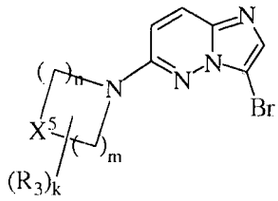
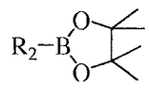
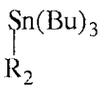
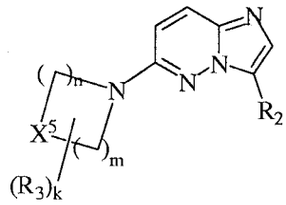
[00026] In certain embodiments of such pharmaceutical compositions, the pharmaceutical compositions are formulated for intravenous, oral administration, rectal administration inhalation, nasal administration, topical administration, ophthalmic administration or otic administration. In certain embodiments of such pharmaceutical compositions, the pharmaceutical composition is 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.

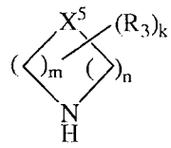
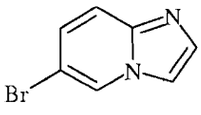
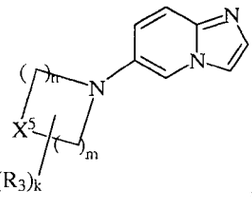
[00027] Another aspect provided herein are medicaments for treating a kinase-mediated disease or condition in a patient wherein the medicament comprises a therapeutically effective amount of a compound of Formula (I), wherein the kinase is selected from Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and ALK.

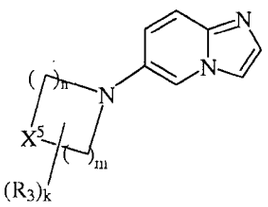
[00028] Another aspect provided herein is the use of a compound of Formula (I) in the manufacture of a medicament for treating a kinase-mediated disease or condition, wherein the kinase is selected from Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and ALK.

[00029] Another aspect provided herein is a method of making any of the aforementioned compounds

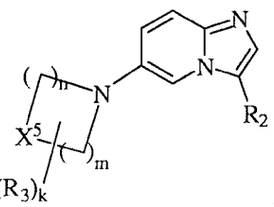
of Formula (I), in which X^1 is N; X^2 is N; X^3 is C and X^4 is C. Such a method comprises: admixing a compound of structure:  with a compound having the structure:  in the presence of KF a to yield a compound having the structure:  , and admixing, in the presence of a palladium catalyst, the compound having the structure:

 with a compound having either the structure: R^2-B(OH)$_2$,  or  to yield a compound having the structure:  .

[00030] Another aspect provided herein is a method of making any of the aforementioned compounds of Formula (I), in which X^1 is CR^9; X^2 is N; X^3 is C and X^4 is C. Such a method comprises: admixing a compound of structure:  with a compound having the structure:  in the presence of a palladium catalyst to yield a compound having the structure:  , and admixing, in the presence of a palladium catalyst, the compound having the structure:

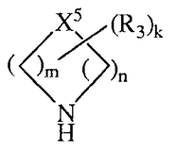


with a compound having the structure: R^2-Br, to yield a compound having the

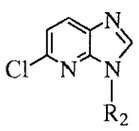


structure:

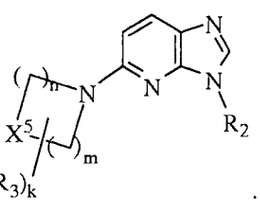
[00031] Another aspect provided herein is a method of making any of the aforementioned compounds of Formula (I), in which X^1 is N; X^2 is C; X^3 is N and X^4 is C. Such a method comprises: admixing a compound of structure:



with a compound having the structure:



in the presence of a palladium catalyst a to yield a compound having the structure:



[00032] Another aspect provided herein are methods for inhibiting a kinase, comprising administering to a system or a subject in need thereof, a therapeutically effective amount of a compound any of Formula (I), or pharmaceutically acceptable salts or pharmaceutical compositions thereof, thereby inhibiting the kinase. In certain embodiments of such methods, the kinase is selected from Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and ALK or a combination thereof. In certain embodiments of such methods the kinase is TrkA, TrkB, TrkC or ALK. In certain embodiments of such methods, the method comprises administering the compound to a cell or tissue system or to a human or animal subject.

[00033] Another aspect provided herein are methods for treating a kinase-mediated disease or condition, 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, thereby treating the condition, and wherein the kinase is selected from Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and ALK or a combination thereof. In certain embodiments of such methods, the method comprises administering the compound to a cell or tissue system; or to a human or animal subject. In certain embodiments of such

methods, the disease or condition is cancer, a proliferative diseases, a pain disorder, a dermatological disease, a metabolic disease, a muscle disease, a neurodegenerative disease, a neurological disease, an immunodeficiency disease, an immunologically-mediated disease, an autoimmune disease, an autoimmune mediated disease, a bone disease, an inflammatory disease, fibrosis, an ophthalmic disease, an infectious disease, a viral disease, wound repair, a respiratory disease, a pulmonary disease, a renal disease, a kidney disease, a liver disease, a cardiovascular disease, a vascular disease, heart disease, cell death and hyperplasiaan inflammatory 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, allergic rhinitis, psoriasis, scleroderma, urticaria, rheumatoid arthritis, multiple sclerosis, lymphoma, metastasis, anaplastic large-cell lymphoma, osteosarcoma, fibrosarcoma, melanoma, breast cancer, renal cancer, brain cancer, prostate cancer, colorectal cancer, thyroid cancer, ovarian cancer, pancreatic cancer, neuronal cancer, neuroblastoma, lung cancer, uterine cancer, gastrointestinal cancer, HIV or lupus.

[00034] Another aspect provided herein are methods 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 Formula (I), or pharmaceutically acceptable salts or pharmaceutical compositions thereof; wherein the cell-proliferative condition is lymphoma, metastasis, anaplastic large-cell lymphoma, osteosarcoma, fibrosarcoma, melanoma, breast cancer, renal cancer, brain cancer, prostate cancer, colorectal cancer, thyroid cancer, ovarian cancer, pancreatic cancer, neuronal cancer, neuroblastoma, lung cancer, uterine cancer or gastrointestinal cancer. In certain embodiments of such methods, the cell-proliferative condition is anaplastic large-cell lymphoma, pancreatic cancer, ovarian cancer and lung cancer.

[00035] Another aspect provided herein are compounds for use in a method of medical treatment, wherein the method of medical treatment is for treating a disease selected from cancer, a proliferative diseases, a pain disorder, a dermatological disease, a metabolic disease, a muscle disease, a neurodegenerative disease, a neurological disease, an immunodeficiency disease, an immunologically-mediated disease, an autoimmune disease, an autoimmune mediated disease, a bone disease, an inflammatory disease, fibrosis, an ophthalmic disease, an infectious disease, a viral disease, wound repair, a respiratory disease, a pulmonary disease, a renal disease, a kidney disease, a liver disease, a cardiovascular disease, a vascular disease, heart disease, cell death and hyperplasiaan inflammatory disease, and wherein the compound is a compound of Formula (I). In certain embodiments of the disease is asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohns disease, bronchitis, dermatitis, allergic rhinitis, psoriasis, scleroderma, urticaria, rheumatoid arthritis, multiple sclerosis, lymphoma, metastasis, anaplastic large-cell lymphoma, osteosarcoma, fibrosarcoma, melanoma, breast cancer,

renal cancer, brain cancer, prostate cancer, colorectal cancer, thyroid cancer, ovarian cancer, pancreatic cancer, neuronal cancer, neuroblastoma, lung cancer, uterine cancer, gastrointestinal cancer, HIV or lupus.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[00036] The terms "alkenyl" and "alkene," 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 or alkene group can be optionally substituted. As used herein, the terms "C_2-C_3alkyenyl", "C_2-C_4alkyenyl", "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. Non-limiting examples of alkenyl groups, as used herein, include ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl and the like. As used herein, the terms "C_2-C_3alkyene", "C_2-C_4alkyene", "C_2-C_5alkene", "C_2-C_6alkene", "C_2-C_7alkene", and "C_2-C_8alkene" refer to an alkene group containing at least 2, and at most 3, 4, 5, 6, 7 or 8 carbon atoms, respectively. Non-limiting examples of alkene groups, as used herein, include ethene, propene, butene, pentene, hexene, heptene, octene, nonene, decene and the like.

[00037] 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. Non-limiting examples of alkenylene groups as used herein include, ethenylene, propenylene, butenylene, pentenylene, hexenylene, heptenylene, octenylene, nonenylene, decenylene and the like.

[00038] 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. 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.

[00039] 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. 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.

[00040] 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. Non-limiting examples of alkynyl groups, as used herein, include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl and the like.

[00041] 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. Non-limiting examples of alkynylene groups as used herein include, ethynylene, propynylene, butynylene, pentynylene, hexynylene, heptynylene, octynylene, nonynylene, decynylene and the like.

[00042] 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.

[00043] 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 with one or more substituents. Non-limiting examples of aryl groups, as used herein, include phenyl, naphthyl, fluorenyl, indenyl, azulenyl, anthracenyl and the like.

[00044] The term "arylene," as used means a divalent radical derived from an aryl group. An arylene group can be optionally substituted.

[00045] The term "cyano," as used herein, refers to a -CN group.

[00046] 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.

[00047] The term "cycloalkylene," as used means a divalent radical derived from a cycloalkyl group. A cycloalkylene group can be optionally substituted.

[00048] The term "halogen," as used herein, refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I).

[00049] The term "halo," as used herein, refers to the halogen radicals: fluoro (-F), chloro (-Cl), bromo (-Br), and iodo (-I).

[00050] 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.

[00051] 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.

[00052] 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.

[00053] 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.

[00054] 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.

[00055] 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 can be optionally substituted with one or more substituents. 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, 1H-benzo[d]imidazol-2(3H)-one, benzo[e][1,3]oxazin-2-one, cinnolinyl, furazanyl, furyl, furopyridinyl, imidazolyl, indolyl, indolizinyl, indolin-2-one, indazolyl, indolin-2-one, isoindolyl, isoquinolinyl, isoxazolyl, isothiazolyl, 1,8-naphthyridinyl, oxazolyl, oxaindolyl, oxadiazolyl, pyrazolyl, pyrrolyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinoxalinyl, quinolinyl, quinazolinyl, 4H-quinolizinyl, quinolin-2(1H)-one, thiazolyl, thiadiazolyl, thienyl, triazinyl, triazolyl and tetrazolyl.

[00056] The term "heteroarylene," as used means a divalent radical derived from a heteroaryl group. A heteroarylene group can be optionally substituted.

[00057] 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, piperazinyl-2-one, 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,

2,5-diazabicyclo[2.2.1]heptane and 3-azabicyclo[4.1.0]heptanyl.

[00058] The term "heterocycloalkylene," as used means a divalent radical derived from a heterocycloalkyl group. A heterocycloalkylene group can be optionally substituted.

[00059] The term "heteroatom," as used herein, refers to one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon.

[00060] The term "hydroxyl," as used herein, refers to the group -OH.

[00061] 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.

[00062] The term "isocyanato," as used herein, refers to a –N=C=O group.

[00063] The term "isothiocyanato," as used herein, refers to a –N=C=S group.

[00064] The term "mercaptyl," as used herein, refers to an (alkyl)S- group.

[00065] 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, –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, -$S(O)_2$R, -NHR, -$N(R)_2$, -NHC(O)R, –NRC(O)R, -NHC(O)OR, -NRC(O)OR, $S(O)_2$NHR, –$S(O)_2N(R)_2$, -$NHS(O)_2$, -$NRS(O)_2$, -$NHS(O)_2$R, -$NRS(O)_2$R, C_1-C_8alkyl, C_1-C_8alkoxy, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, halo-substituted C_1-C_8alkyl, 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 substitutent 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.

[00066] 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.

[00067] 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.

[00068] The term "administration" or "administering" of the subject compound means providing a

compound of the invention and prodrugs thereof to a subject in need of treatment.

[00069] The term "bone disease,` as used herein, refers to a disease or condition of the bone, including, but not limited to, inapproriate bone remodeling, loss or gain, osteopenia, osteomalacia, osteofibrosis, and Paget's disease.

[00070] The term "cardiovascular disease," as used herein refers to diseases affecting the heart or blood vessels or both, including but not limited to: arrhythmia; atherosclerosis and its sequelae; angina; myocardial ischemia; myocardial infarction; cardiac or vascular aneurysm; vasculitis, stroke; peripheral obstructive arteriopathy of a limb, an organ, or a tissue; reperfusion injury following ischemia of the brain, heart or other organ or tissue; endotoxic, surgical, or traumatic shock; hypertension, valvular heart disease, heart failure, abnormal blood pressure; shock; vasoconstriction (including that associated with migraines); vascular abnormality, inflammation, insufficiency limited to a single organ or tissue.

[00071] 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).

[00072] 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.

[00073] 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.

[00074] 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, and urticaria.

[00075] 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.

[00076] 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.

[00077] 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.

[00078] 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.

[00079] The term "iatrogenic", as used herein, means a condition, disorder, or disease created or worsened by medical or surgical therapy.

[00080] 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, temporarl arteritis); joints (arthritis: crystalline, osteo-, psoriatic, reactive, rheumatoid, Reiter's); gastrointestinal tract (Disease,); skin (dermatitis); or multiple organs and tissues (systemic lupus erythematosus).

[00081] The term "Kinase Panel", as used herein, refers to is a list of kinases including but not limited to Abl(human), Abl(T315I), JAK2, JAK3, ALK, JNK1α1, ALK4, KDR, Aurora-A, Lck, Blk, MAPK1, Bmx, MAPKAP-K2, BRK, MEK1, CaMKII(rat), Met, CDK1/cyclinB, p70S6K, CHK2, PAK2, CK1, PDGFRα, CK2, PDK1, c-Kit, Pim-2, C-Raf, PKA(h), CSK, PKBα, Src, PKCα, DYRK2, Plk3, EGFR,

ROCK-I, Fes, Ron, FGFR-3, Ros, Flt3, SAPK2α, Fms, SGK, Fyn, SIK, GSK3β, Syk, IGFR, Tie-2, IKKß, IR, WNK3, IRAK4, ZAP-70, ITK, AMPK(rat), LIMK1, Rsk2, Axl, LKB1, SAPK2β, BrSK2, Lyn (h), SAPK3, BTK, MAPKAP-K3, SAPK4, CaMKIV, MARK1, Snk, CDK2/cyclinA, MINK, SRPK1, CDK3/cyclinE, MKK4(m), TAK1, CDK5/p25, MKK6(h), TBK1, CDK6/cyclinD3, MLCK, TrkA, TrkB, TrkC, CDK7/cyclinH/MAT1, MRCKβ, TSSK1, CHK1, MSK1, Yes, CK1d, MST2, ZIPK, c-Kit (D816V), MuSK, DAPK2, NEK2, DDR2, NEK6, DMPK, PAK4, DRAK1, PAR-1Bα, EphA1, PDGFRβ, EphA2, Pim-1, EphA5, PKBβ, EphB2, PKCβI, EphB4, PKCδ, FGFR1, PKCη, FGFR2, PKCθ, FGFR4, PKD2, Fgr, PKG1β, Flt1, PRK2, Hck, PYK2, HIPK2, Ret, IKKα, RIPK2, IRR, ROCK-II(human), JNK2α2, Rse, JNK3, Rsk1(h), PI3 Kγ, PI3 Kδ and PI3-Kβ.

[00082] 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.

[00083] 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 and an antagonist.

[00084] The terms "neurogenerative disease" or "nervous system disorder," as used herein, refers to conditions that alter the structure or function of the brain, spinal cord or peripheral nervous system, including but not limited to Alzheimer's Disease, cerebral edema, cerebral ischemia, multiple sclerosis, neuropathies, Parkinson's Disease, those found after blunt or surgical trauma (including post-surgical cognitive dysfunction and spinal cord or brain stem injury), as well as the neurological aspects of disorders such as degenerative disk disease and sciatica. The acronym "CNS" refers to disorders of the central nervous system (brain and spinal cord).

[00085] 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, pappillary conjunctivitis.

[00086] 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.

[00087] 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.

[00088] The term "pharmaceutical combination" as used herein means 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, e.g. a compound of Formula I and a coagent, 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, e.g. a compound of Formula I and a co-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.

[00089] The term "pharmaceutical composition", as used herein, refers to a mixture of a compound described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients.

[00090] The term "prodrug", as used herein, refers to an agent that is converted into the parent drug in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. Prodrugs are bioavailable by oral administration whereas the parent is not. Prodrugs improve solubility in pharmaceutical compositions over the parent drug. 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.

[00091] 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.

[00092] 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.

[00093] 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.

[00094] 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.

[00095] The terms "use" or "used," as used herein, are intended to include a compound of Formula (I) provided herein for use in the prophylactic and/or therapeutic treatment of one or more diseases provided herein, a method of use or a method of treatment comprising administering a compound of the Formula (I) to a person in need of such treatment in an effective amount for the prophylactic and/or therapeutic treatment of one or more diseases provided herein, the preparation or a method or preparation of a pharmaceutical formulation/preparation for use in the prophylactic and therapeutic treatment of one or more diseases provided herein, especially involving mixing a compound of the Formula (I) (as therapeutically active ingredient) with at least one pharmaceutically acceptable carrier material, including making it ready for use in such treatment (e.g. adding an instruction insert (e.g. package leaflet or the like), formulation, appropriate preparation, adaptation for specific uses, customizing and the like), and the use of a compound of the Formula (I) for such preparation, and/or all other prophylactic or therapeutic uses mentioned herein.

[00096] Other objects, features and advantages of the methods and compositions 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.

Compounds

[00097] Provided herein are compounds, pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, which are modulators of kinase activity. Provided herein are compounds, pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, which are modulators of protein kinases. Also provided herein are compounds, pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, pharmaceutical combinations and

methods for the treatment and/or prevention of protein kinase related diseases or conditions/disorders, including disease or conditions/disorders associated with abnormal or deregulated protein kinase activity. In certain embodiments, compounds, pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, provided herein are modulators of Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK protein kinases. In certain embodiments, compounds, pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, provided herein are inhbitors of Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK protein kinases. In certain embodiments, compounds, pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, provided herein are inhbitors of TrkA, TrkB, TrkC, IGF-1R, and/or ALK protein kinases. In other embodiments, the compounds, pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, provided herein are used to treat and/or prevent diseases and conditions related to, or mediated by, Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGR-1R, ALK4, ALK5, ALK or a combination thereof. In other embodiments, the compounds, pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, provided herein are used to treat and/or prevent diseases and conditions related to, or mediated by, TrkA, TrkB, TrkC, IGR-1R, ALK protein kinases or a combination thereof.

[00098] Further provided herein are compounds, pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions containing such pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, for the treatment and/or prevention of diseases and/or disorders in which aberrant, abnormal or deregulated activity of Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGR-1R, ALK4, ALK5, or ALK protein kinase contributes to the pathology and/or symptomology of such diseases and/or disorders. Also provided herein are compounds, pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions containing such pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, for the treatment and/or prevention of diseases and/or disorders in which aberrant, abnormal or deregulated activity of TrkA, TrkB, TrkC, IGR-1R, or ALK protein kinase contributes to the pathology and/or symptomology of such diseases and/or disorders.

[00099] In certain embodiments, such diseases and/or disorders include, but are not limited to, cancer, proliferative diseases, pain, dermatological diseases and/or disorders, metabolic diseases and/or disorders, muscle diseases and/or disorders, neurodegenerative diseases and/or disorders, neurological diseases and/or disorders, immunodeficiency diseases and/or disorders, immunologically-mediated diseases and/or disorders, autoimmune diseases, autoimmune mediated diseases, bone diseases and/or disorders, inflammatory diseases, fibrosis, ophthalmic/occular diseases and/or disorders, infectious diseases, viral diseases, wound repair, respiratory diseases and/or disorders, pulmonary diseases and/or disorders, renal

disease, kidney disease, liver disease, cardiovascular diseases and/or disorders, vascular diseases and/or disorders heart disease, cell death and hyperplasia.

[000100] Such cancer and proliferative diseases include, but are not limited to, hematopoietic disorders, hematopoietic malignancies, non-hematopoietic malignancies, benign or malignant tumors, tumors of the neck and head, brain cancer, kidney cancer, liver cancer, adrenal gland cancer, neuronal cancer, neuroblastoma, bladder cancer, breast cancer, secretory breast carcinoma, stomach cancer, gastric tumors, ovarian cancer, uterine cancer, colon cancer, rectal cancer, colorectal adenoma, prostate cancer, renal cancer, brain cancer, endometrial cancer, pancreatic cancer, lung cancer, non-small cell lung cancer, human adenoid cystic carcinoma, vaginal cancer, thyroid cancer, papillary thyroid carcinoma, sarcoma, congenital fibrosarcoma, osteolytic sarcoma, osteosarcoma, fibrosarcoma, myeloma, tumor metastasis to bone, congenital mesoblastic nephroma, glioblastomas, melanoma, multiple myeloma, gastrointestinal cancer, gastrointestinal stromal tumors (GIST), mastocytosis, neuroblastoma, fibrotic cancers, tumor metastasis growth, epidermal hyperproliferation, psoriasis, metastasis, prostate hyperplasia, neoplasia, neoplasia of epithelial character, lymphomas, diffuse large B-cell lymphoma, B-cell lymphoma, mammary carcinoma, Wilm's tumor, Cowden syndrome, Lhermitte-Dudos disease and Bannayan-Zonana syndrome.

[000101] Such hematopoietic disorders include, but are not limited to, myeloproliferative disorders, thrombocythemia, essential thrombocytosis (ET), angiogenic myeloid metaplasia, myelofibrosis (MF), myelofibrosis with myeloid metaplasia (MMM), chronic idiopathic myelofibrosis (IMF), polycythemia vera (PV), the cytopenias, and pre-malignant myelodysplastic syndromes.

[000102] Such hematological malignancies include, but are not limited to, leukemias, myeloid leukemias, hairy cell leukemia, lymphomas (non-Hodgkin's lymphoma), Hodgkin's disease (also called Hodgkin's lymphoma), and myeloma, including, but are not limited to, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL), anaplastic large-cell lymphoma (ALCL), prolymphocytic leukemia (PML), juvenile myelomonocyctic leukemia (JMML), adult T-cell ALL, AML with trilineage myelodysplasia (AML/TMDS), mixed lineage leukemia (MLL), myelodysplastic syndromes (MDSs), myeloproliferative disorders (MPD), multiple myeloma, (MM), myeloid sarcoma and acute promyelocytic leukemia (APL).

[000103] Such pain disorders include, but are not limited to, cancer-related pain, skeletal pain caused by tumor metastasis, osteoarthritis, visceral pain, inflammatory pain and neurogenic pain.

[000104] Such dermatological diseases and/or disorders include, but are not limited to, inflammatory or allergic conditions of the skin, dermatitis, eczema, psoriasis, atopic dermatitis, seborrhoeic dermatitis (Dandruff, Cradle cap), diaper rash, urushiol-induced contact dermatitis, contact dermatitis, erythroderma, lichen simplex chronicus, prurigo nodularis, itch, pruritus ani, nummular dermatitis, dyshidrosis, pityriasis alba, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity

angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphigus, epidermolysis bullosa acquisita, peritoneal and sub dermal adhesion and photoaging of the skin.

[000105] Such metabolic diseases and/or disorders and eating disorder include, but are not limited to, obesity, diabetes and anoerexia.

[000106] Such muscle diseases and/or disorders include, but are not limited to, muscular atrophies (e.g. disuse), muscular dystrophies (e.g. Duchenne's muscle dystrophy, Becker's muscle dystrophy, Limb-Girdle muscle dystrophy), sarcopenia, cachexia, wasting and Facioscapulohumeral dystrophy.

[000107] Such neurological diseases and/or disorders and neurodegenerative disorders include, but are not limited to, impaired neurological function and Alzheimer's disease.

[000108] Such immunodeficiency diseases and/or disorders and immunologically-mediated diseases and/or disorders include, but are not limited to, pathologic immune conditions involving T cell activation, anaphylaxis, allergy and psoriasis. Such allergy disorders include, but are not limited to, respiratory diseases and dermatolgical disorders.

[000109] Such autoimmune diseases and/or disorders and autoimmune -mediated diseases and/or disorders include, but are not limited to, destructive arthritis, rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, multiple sclerosis, dermatomyositis, progressive systemic sclerosis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or aetiology, including autoimmune haematological disorders (e.g. haemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), primary binary cirrhosis (PBC), lupus, systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary billiary cirrhosis, uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

[000110] Such bone diseases and/or disorders include, but are not limited to, osteoporosis, osteitis deformans, Paget's disease, osteoarthritis, prosthesis failure, osteopenia, and fractures and other disorders in which low bone mineral density are a hallmark of the disease.

[000111] Such inflammatory diseases and/or disorders include, but are not limited to, uveitis, atherosclerosis, atherogenesis, glomerulonephritis, Kawasaki disease, inflammatory responses, polymyositis, arthritis, neurological inflammation, chronic arthritis inflammation and osteoarthritis.

[000112] Such fibrosis diseases and/or disorders include, but are not limited to, extracellular matrix accumulation and fibrosis, scleroderma, fibrosclerosis, radiation-induced fibrosis, kidney fibrosis, lung

fibrosis and liver fibrosis, haemochromatosis, primary biliary cirrhosis, restenosis, retroperitoneal fibrosis, mesenteric fibrosis, endometriosis and keloids.

[000113] Such ophthalmic/ocular diseases and/or disorders include, but are not limited to, proliferative vitreoretinopathy, ocular scarring, corneal scarring, ocular disorders, corneal wounds, conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis.

[000114] Such infectious and viral diseases and/or disorders include, but are not limited to, HIV-1 infection, for example, hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-induced hepatitis.

[000115] Wound repair includes, but are not limited to, excessive or hypertrophic scar or keloid formation in the dermis occurring during wound healing resulting from trauma or surgical wounds, ulcers (including diabetic ulcers, chronic ulcers, gastric ulcers, and duodenal ulcers).

[000116] Such respiratory diseases and/or disorders and pulmonary disorders include, but are not limited to, asthma, bronchial asthma, allergic asthma, intrinsic (non-allergic) asthma, extrinsic (allergic) asthma, exercise-induced asthma, drug-induced asthma (including aspirin and NSAID-induced) and dust-induced asthma, chronic obstructive pulmonary disease (COPD); chronic obstructive airways disease (COAD), chronic obstructive lung disease (COLD), bronchitis, chronic bronchitis, acute bronchitis, dyspnea, arachidic bronchitis, catarrhal bronchitis, croupus bronchitis, phthinoid bronchitis, rhinitis, acute rhinitis, chronic rhinitis, rhinitis medicamentosa, vasomotor rhinitis, perennial and seasonal allergic rhinitis, rhinitis nervosa (hay fever), inflammatory or obstructive airways diseases, pulmonary hypertension, acute lung injury, adult/acute respiratory distress syndrome (ARDS), pulmonary fibrosis, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, pulmonary disease due to infectious or toxic agents, emphysema, pneumoconiosis, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis, byssinosis, acute lung injury (ALI), hypereosinophilia, Löffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma, eosinophil-related disorders affecting the airways occasioned by drug-reaction, pulmonary hypertension, primary pulmonary hypertension (PPH), secondary pulmonary hypertension (SPH), familial PPH, sporadic PPH, precapillary pulmonary hypertension, pulmonary arterial hypertension (PAH), pulmonary artery hypertension, idiopathic pulmonary hypertension, thrombotic pulmonary arteriopathy (TPA), plexogenic pulmonary arteriopathy, functional classes I to IV pulmonary hypertension, and pulmonary hypertension associated with, related to, or secondary to, left ventricular dysfunction, mitral valvular disease, constrictive pericarditis, aortic stenosis, cardiomyopathy, mediastinal fibrosis, anomalous pulmonary venous drainage, pulmonary venoocclusive disease, collagen vascular disease, congenital heart disease, HIV virus infection, drugs and toxins such as fenfluramines, hypoxemia, pulmonary venous hypertension, chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorder, chronic exposure to high altitude, neonatal lung disease, alveolar-capillary dysplasia, sickle cell disease,

other coagulation disorder, chronic thromboemboli, connective tissue disease, lupus, schistosomiasis, sarcoidosis or pulmonary capillary hemangiomatosis.

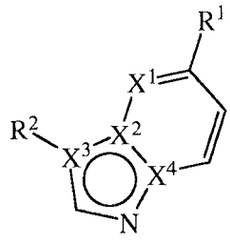
[000117] Such renal diseases and/or disorders include, but are not limited to, glomerulonephritis, renal interstitial fibrosis, renal fibrosis, chronic renal disease and acute renal disease. Such kidneey diseases and/or disorders include, but are not limited to, diabetic nephropathy, lupus nephritis, hypertension-induced nephropathy, HIV-associated nephropathy and transplant necropathy. Such liver diseases and/or disorders include, but are not limited to, hepatic dysfunction attributable to infections, alcohol- induced hepatitis, disorders of the biliary tree and hepatic ischemia.

[000118] Such cardiovascular, vascular or heart diseases and/or disorders include, but are not limited to, congestive heart failure, post-infarction cardiac fibrosis, congestive heart failure, reperfusion/ischemia in stroke, heart attacks, and organ hypoxia, ischemia, dilated cardiomyopathy, myocarditis, myocardial infarction vascular stenosis, restenosis, atherosclerosis, male erectile dysfunction, Raynaud's syndrome, thrombosis and thrombin-induced platelet aggregation.

[000119] In other embodiments the compounds of Formula (I) provided herein are immunosuppressive agents and are used to treat organ transplant rejection, chronic transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, dermatitis, Crohn's disease, type-1 diabetes and complications from type-1 diabetes.

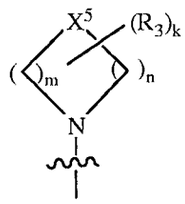
[000120] In certain embodiments, the compounds, pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions and pharmaceutical combinations provided herein are inhibitors of Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGR-1R, ALK4, ALK5, and/or ALK protein kinase activity.

[000121] The aforementioned compounds and pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, are compounds having structures according to Formula (I),



Formula (I)

wherein:

R^1 is  ; wherein,

X^1, X^2 X^3 and X^4 are each independently CR^9, C or N, with the proviso that at least one of X^1, X^2 X^3 and X^4 is N and at most only two of X^1, X^2 X^3 and X^4 are N;

X^5 is $C(R^3)_2$, O, S, $S(O)_2$, S(O), or N;

m is 1, 2, 3 or 4;

n is 0, 1, 2 or 3;

k is 0, 1, 2, 3, 4, 5 or 6;

each R^3 is independently selected from halogen, nitro, $-N(R^4)_2$, $-OR^9$, -CN, =O, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-C(O)OR^9$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, $-OC(O)R^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, C_1-C_8alkyl, C_6-C_{14}aryl, C_3-C_8cycloalkyl, halo-substituted-C_1-C_8alkyl, C_1-C_8alkoxy, hydroxyl-C_1-C_8alkyl, halo-substituted C_1-C_8alkoxy, C_2-C_{14}heterocycloalkyl and C_2-C_{13}heteroaryl, wherein the C_1-C_8alkyl, C_6-C_{14}aryl, C_3-C_8cycloalkyl, C_2-C_{14}heterocycloalkyl and C_2-C_{13}heteroaryl of R^3 are optionally substituted with 1 to 3 substituents independently selected from halogen, amino, nitro, hydroxyl, cyano, $-OR^9$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-C(O)OR^9$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, $-OC(O)R^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, C_1-C_8alkyl, C_1-C_8aminoalkyl, C_1-C_8alkoxy, C_1-C_8alkylthio, hydroxyl-C_1-C_8alkyl, halo-substituted-C_1-C_8alkyl, halo-substituted-C_1-C_8alkoxy, C_3-C_8cycloalkyl, C_2-C_{14}heterocycloalkyl, C_6-C_{14}aryl and C_2-C_{13}heteroaryl;

alternatively each R^3 is independently a C_1-C_8alkyl, wherein at least two R^3 together form a C_3-C_8cycloalkyl fused with a heterocycle and wherein each C_1-C_8alkyl of R^3 is optionally substituted with 1 to 3 substituents independently selected from halogen, amino, nitro, hydroxyl, cyano, $-OR^9$, C_1-C_8alkyl, C_1-C_8aminoalkyl, C_1-C_8alkoxy, C_1-C_8alkylthio, hydroxyl-C_1-C_8alkyl, halo-substituted-C_1-C_8alkyl, halo-substituted-C_1-C_8alkoxy, C_3-C_8cycloalkyl, C_2-C_{14}heterocycloalkyl, C_6-C_{14}aryl and C_2-C_{13}heteroaryl;

R^2 is C_6-C_{14}aryl, C_2-C_{13}heteroaryl or C_2-C_{14}heterocycloalkyl, wherein the C_6-C_{14}aryl, C_2-C_{13}heteroaryl or C_2-C_{14}heterocycloalkyl of R^2 are optionally substituted with 1 to 3 substituents independently selected from halogen, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-OC(O)R^9$, C_1-C_8alkoxy, hydroxyl-C_1-C_8alkyl, halo-substituted C_1-C_8alkyl and halo-substituted C_1-C_8alkoxy;

each R^4 is independently selected from H, C_1-C_8 alkyl, $-L^1R^5$, $-L^1R^6$, $-L^1R^8$, C_2-C_{13}heteroaryl, C_6-C_{14}aryl, C_2-C_{14}heterocycloalkyl and C_3-C_8cycloalkyl, wherein the C_1-C_8alkyl, C_2-C_{13}heteroaryl and C_3-C_8cycloalkyl are optionally substituted with 1 to 3 substituents independently selected from halogen, deuterium, $-CD_3$, $-S(O)_2R^9$, -CN, C_1-C_8alkyl, $-OR^9$, $-N(R^9)_2$ and $-(CH_2)_pOR^9$;

L^1 is a bond, C_1-C_8alkylene, C_2-C_8alkenylene, $-O(CH_2)_p$-, -C(O)-, $-N(R^9)$-, $(CH_2)_pC(O)$-, $-C(O)(CH_2)_pO(CH_2)_p$- or -C(O)O-;

Y^1 is C_6-C_{14}arylene, C_2-C_{13}heteroarylene, C_3-C_8cycloalkylene, C_2-C_{14}heterocycloalkylene or C_1-C_8alkoxylene, each of which is optionally substituted with 1 to 3 substituents independently selected from halogen, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-OC(O)R^9$, C_1-C_8alkoxy, hydroxyl-C_1-C_8alkyl, halo-substituted C_1-C_8alkyl and halo-substituted C_1-C_8alkoxy;

R^5 is C_6-C_{14}aryl, C_2-C_{13}heteroaryl, C_2-C_{14}heterocycloalkyl, $-N(R^9)_2$, $-N(R^9)C(O)R^9$, $-C(O)N(R^9)_2$, $-(CH_2)_pOR^9$ or $-OR^9$.

R^6 is C_6-C_{14}aryl, C_2-C_{13}heteroaryl, C_2-C_{14}heterocycloalkyl, $-OCH(R^7)_2$, $-C(O)R^7$, C_1-C_8alkyl, or C_3-C_8cycloalkyl, wherein the C_1-C_8alkyl, C_3-C_8cycloalkyl, C_6-C_{14}aryl, C_2-C_{13}heteroaryl, and C_2-C_{14}heterocycloalkyl of R^6 are optionally substituted with 1 to 3 substituents independently selected from halogen, $-CN$,$-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^8$, $OC(O)N(R^4)_2$, $-N(R^9)_2$, $-C(O)C(O)OR^9$, $-(CH_2)_pN(R^9)_2$, $-N(R^4)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-(CH_2)_pS(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-NR^4S(O)_2R^9$, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_2-C_8alkene, C_1-C_8alkoxy, hydroxyl-substituted C_1-C_8alkyl, halo-substituted C_1-C_8alkyl and halo-substituted C_1-C_8alkoxy;

or R^6 is C_6-C_{14}aryl, C_2-C_{13}heteroaryl, C_2-C_{14}heterocycloalkyl or C_3-C_8cycloalkyl having a C_1-C_4alkyl bridge;

or R^6 is a C_2-C_{14}heterocycloalkyl optionally substituted with 1 to 3 substituents independently selected from halogen, =O, –CN,–OR^9, -$(CH_2)_pOR^9$, -$L^1C(O)R^8$, -L^1R^8, -L^1R^5, -$C(O)R^9$, -$OC(O)R^9$, -$C(O)OR^9$, -$C(O)R^8$, $OC(O)N(R^4)_2$, -$N(R^9)_2$, -$C(O)C(O)OR^9$, –$(CH_2)_pN(R^9)_2$, -$N(R^4)_2$, –$C(O)N(R^4)_2$, –$N(R^4)C(O)R^4$, –$N(R^4)C(O)OR^4$, –$(CH_2)_pS(O)_2R^9$, –$S(O)_2R^9$, –$S(O)_2N(R^4)_2$, –$NR^4S(O)_2R^4$, –$NR^4S(O)_2R^9$, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_2-C_8alkene, C_1-C_8alkoxy, hydroxyl-substituted C_1-C_8alkyl, halo-substituted C_1-C_8alkyl and halo-substituted C_1-C_8alkoxy;

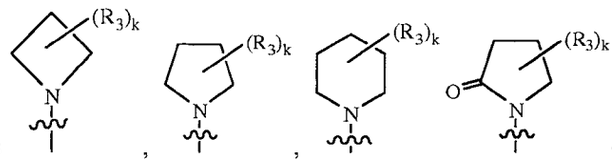
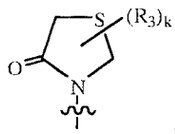
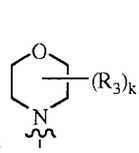
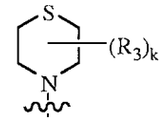
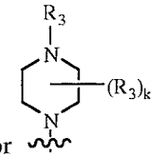
each R^7 is independently selected from H, C_1-C_8alkyl and -L^1R^8;

R^8 is H, -$N(R^9)_2$, -$N(R^4)_2$, -SR^9, -CN, C_1-C_8alkyl, C_3-C_8cycloalkyl and C_2-C_{14}heterocycloalkyl, wherein the C_1-C_8alkyl, C_3-C_8cycloalkyl and C_2-C_{14}heterocycloalkyl of R^8 are optionally substituted with 1 to 3 substituents independently selected from halogen, C_1-C_6alkyl, –CN,–OR^9, -$(CH_2)_pOR^9$, -$L^1C(O)R^8$, -$C(O)R^9$, -$OC(O)R^9$, -$C(O)OR^9$, -$N(R^9)_2$, -$N(R^4)_2$, –$C(O)N(R^4)_2$, –$N(R^4)C(O)R^4$, –$N(R^4)C(O)OR^4$, –$S(O)_2R^9$, –$S(O)_2N(R^4)_2$, and –$NR^4S(O)_2$;

each R^9 is independently selected from H, C_3-C_8cycloalkyl and C_1-C_8alkyl,

and

each p is independently 1, 2, 3, 4, 5 or 6.

[000122] In certain embodiments R^1 is  , , , or  , while in other embodiments R^1 is  ,  ,  or .

[000123] In certain embodiments each R^3 is independently selected from halo, -OR^9, C_1-C_8alkyl, C_6-C_{14}aryl, C_3-C_8cycloalkyl, halo-substituted-C_1-C_8alkyl, C_2-C_{14}heterocycloalkyl and C_2-C_{13}heteroaryl, wherein the C_1-C_8alkyl, C_6-C_{14}aryl, C_3-C_8cycloalkyl, C_2-C_{14}heterocycloalkyl and C_2-C_{13}heteroaryl of R^3 are optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, -OR^9, C_1-C_8alkyl, C_1-C_8alkoxy, hydroxyl-C_1-C_8alkyl, halo-substituted-C_1-C_8alkyl, halo-substituted-C_1-C_8alkoxy and C_3-C_8cycloalkyl.

[000124] In certain embodiments the C_6-C_{14}aryl of R^3 is phenyl optionally substituted with 1 to 3

substituents independently selected from halo, C_1-C_8alkyl, and halo-substituted-C_1-C_8alkyl.

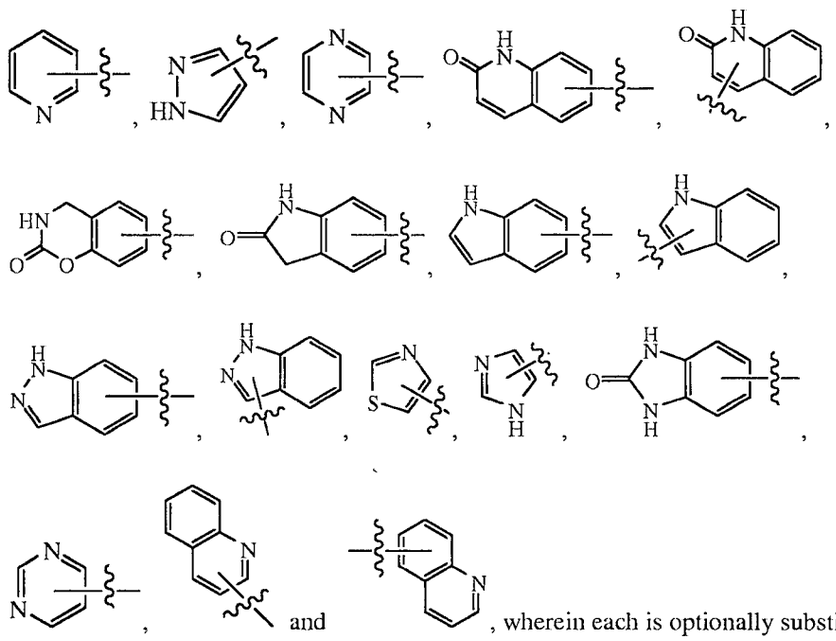
[000125] In certain embodiments the C_6-C_{14}aryl of R^3 is phenyl optionally substituted with 1 to 3 substituents independently selected from fluoro and C_1-C_8alkyl.

[000126] In certain embodiments R^2 is C_6-C_{14}aryl or C_2-C_{13}heteroaryl, wherein the C_6-C_{14}aryl and C_2-C_{13}heteroaryl of R^2 are optionally substituted with 1 to 3 substituents independently selected from halo, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-OC(O)R^9$, C_1-C_8alkoxy, hydroxyl-C_1-C_8alkyl, halo-substituted C_1-C_8alkyl and halo-substituted C_1-C_8alkoxy.

[000127] In certain embodiments R^2 is C_6-C_{14}aryl or C_2-C_{13}heteroaryl, wherein the C_6-C_{14}aryl and C_2-C_{13}heteroaryl of R^2 are optionally substituted with 1 to 3 substituents independently selected from halo, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ and $-S(O)_2R^9$.

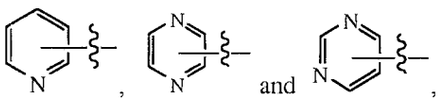
[000128] In certain embodiments the C_6-C_{14}aryl of R^2 is phenyl optionally substituted with 1 to 3 substituents independently selected from halo, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ and $-S(O)_2R^9$.

[000129] In certain embodiments the C_2-C_{13}heteroaryl of R^2 is selected from



and , wherein each is optionally substituted with 1 to 3 substituents independently selected from halo, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ and $-S(O)_2R^9$.

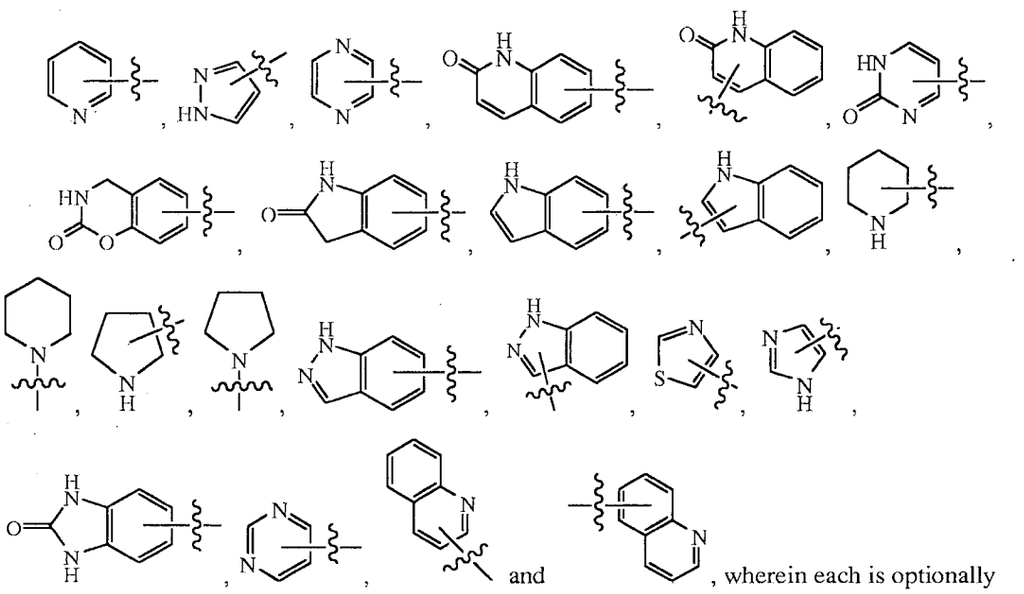
[000130] In certain embodiments of the aforementioned compounds of Formula (I), the C_2-C_{13}heteroaryl of R^2 is selected from



, wherein each is optionally substituted with 1 to 3 substituents independently selected from halogen, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ and $-S(O)_2R^9$.

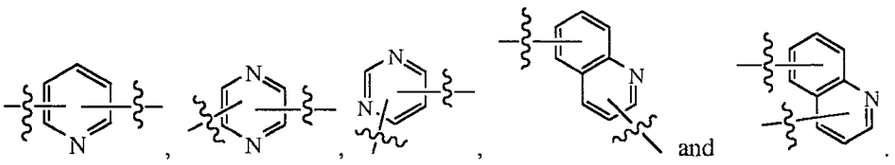
[000131] In certain embodiments of the aforementioned compounds of Formula (I), R^6 is C_2-C_{13}heteroaryl, C_2-C_{14}heterocycloalkyl, $-OCH(R^7)_2$, C_1-C_8alkyl, or C_3-C_8cycloalkyl, wherein the C_1-C_8alkyl, C_3-C_8cycloalkyl, C_2-C_{13}heteroaryl, and C_2-C_{14}heterocycloalkyl of R^6 are optionally substituted with 1 to 3 substituents independently selected from halogen, $-CN$, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-N(R^4)_2$, $-S(O)_2R^9$, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_2-C_8alkene, and hydroxyl-substituted C_1-C_8alkyl.

[000132] In certain embodiments of the aforementioned compounds of Formula (I), R^6 is selected from



, wherein each is optionally substituted with 1 to 3 substituents independently selected from halogen, $-CN$, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-N(R^4)_2$, $-S(O)_2R^9$, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_2-C_8alkene, and hydroxyl-substituted C_1-C_8alkyl.

[000133] In certain embodiments of the aforementioned compounds of Formula (I), Y^1 is C_6-C_{14}arylene or C_2-C_{13}heteroarylene , while in other embodiments Y^1 is selected from



[000134] In certain embodiments of the aforementioned compounds of Formula (I), each R^4 is independently selected from H, C_1-C_8 alkyl, C_6-C_{14}aryl , C_2-C_{14}heterocycloalkyl, -L^1R^5, -L^1R^6 and C_3-C_8cycloalkyl, wherein the C_1-C_8alkyl, C_6-C_{14}aryl , C_2-C_{14}heterocycloalkyl, and C_3-C_8cycloalkyl are optionally substituted with -$(CH_2)_pOR^9$.

[000135] In certain embodiments of the aforementioned compounds of Formula (I), R^5 is C_6-C_{14}aryl, C_2-C_{13}heteroaryl, C_2-C_{14}heterocycloalkyl, -$N(R^9)_2$, –$N(R^9)C(O)R^9$, -$(CH_2)_pOR^9$, or -OR^9.

[000136] In certain embodiments of the aforementioned compounds of Formula (I), R^7 is -L^1R^8. In certain embodiments of the aforementioned compounds of Formula (I), R^8 is -$N(R^9)_2$ or –CN.

[000137] The compounds, 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 of the invention 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 of the invention and pharmaceutically acceptable salts thereof include but are not limited to isotopes of hydrogen, carbon, nitrogen and oxygen such as ^2H, ^3H, ^{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 of the invention and pharmaceutically acceptable salts thereof, for example, those in which a radioactive isotope such as ^3H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. In particular examples, ^3H and ^{14}C isotopes may be used for their ease of preparation and detectability. In other examples, substitution with isotopes such as ^2H 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. Isotopic variations of the compounds have the potential to change a compound's metabolic fate and/or create small changes in physical properties such as hydrophobicity, and the like. Isotopic variation have the potential to enhance efficacy and safety, enhance bioavailability and half-life, alter protein binding, change biodistribution, increase the proportion of active metabolites and/or decrease the formation of reactive or toxic metabolites.

Processes for Making Compounds of Formula (I)

[000138] General procedures for preparing compounds of Formula (I) are described in the Examples,

infra. In the reactions described, reactive functional groups, for example hydroxyl, 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).

[000139] 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.

[000140] The pharmaceutically acceptable organic acid or inorganic acids used to form pharmaceutically acceptable acid addition salts of compounds of Formula (I) include, but are not limited to, hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid, formic acid, acetic acid, trifluoroacetic acid, propionic acid, butyric acid, caprylic acid, dichloroacetic acid, hippuric acid, lactic acid, citric acid, tartaric acid, malic acid, gluconic acid, mandelic acid, maleic acid, succinic acid, adipic acid, aspartic acid, fumaric acid, glutamic acid, malonic acid, sebacic acid, salicylic acid, hexanoic acid, benzoic acid, p-chloro-benzoic acid, nicotinic acid, diphenylacetic acid, triphenylacetic acid, o-hydroxybenzoic acid, p-hydroxybenzoic acid, 1-hydroxynaphthalene-2-carboxylic acid or 3-hydroxynaphthalene-2-carboxylic acid, sulfonic acids, methanesulfonic acid, benzenesulfonic acid, ethanesulfonic acid, ethane-1,2-disulfonic acid, 2-hydroxy-ethanesulfonic acid, (+) camphor-10-sulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid and p-toluenesulfonic acid. Pharmaceutically acceptable solvates are generally hydrates.

[000141] 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.

[000142] Such pharmaceutically acceptable base addition salt of a compound of Formula (I) include, but are not limited to, aluminium, ammonium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine, ethanolamines, benzylamines, pyridine, benethamine, diethanolamine, 4-(2-hydroxy-ethyl)morpholine,1-(2-hydroxyethyl)pyrrolidine, N-methyl glutamine, piperazine, triethanol-amine and zinc salts.

[000143] 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).

[000144] In certain embodiments, the compounds of Formula (I) described herein 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.

[000145] In certain embodiments, prodrug derivatives of compounds Formula (I) described herein 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).

[000146] In certain embodiments, the compounds of Formula (I) described herein 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.

[000147] In certain embodiments, the compounds of Formula (I) described herein 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.

[000148] In certain embodiments, the compounds of Formula (I) provided herein are prepared as a racemic mixture. In certain embodiments, the compounds of Formula (I) described herein are prepared as their individual stereoisomers. In certain embodiments, the compounds of Formula (I) provided herein are

prepared as a racemic mixture and their individual stereoisomers are aobtained using chiral chromatography, including , but not limited to, chiral liquid chromatogtaphy. 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.

[000149] Compounds of Formula (I) are provided in substantially pure form. In certain embodiments compounds of Formula (I) are at least 60% pure. In certain embodiments compounds of Formula (I) are at least 75% pure. In certain embodiments compounds of Formula (I) are at 85% pure. In certain embodiments compounds of Formula (I) are at least 98% pure (% are on a weight for weight basis).

[000150] 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 the invention into a pharmaceutically acceptable salt;

(c) optionally converting a salt form of a compound of the invention to a non-salt form;

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

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

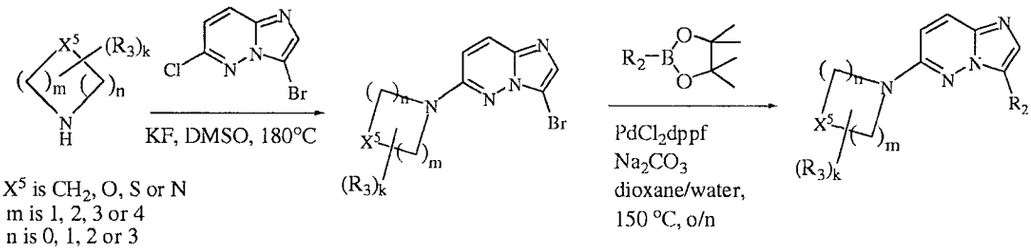
(f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

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

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

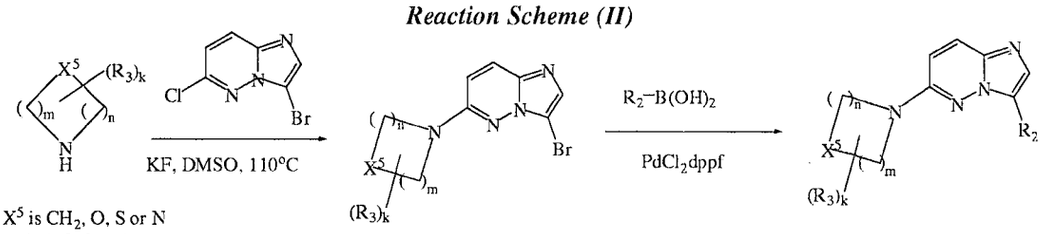
[000151] Non-limiting examples of synthetic schemes used to make compounds of Formula (I) described herein are illustrated in reaction schemes (I)-(V), wherein n, m, k, X^5, R^2 and R^3 are as defined herein.

Reaction Scheme (I)



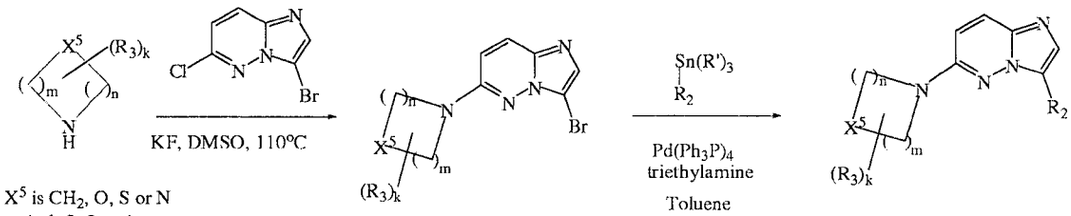
X^5 is CH_2, O, S or N
m is 1, 2, 3 or 4
n is 0, 1, 2 or 3

Reaction Scheme (II)



X^5 is CH_2, O, S or N
m is 1, 2, 3 or 4
n is 0, 1, 2 or 3

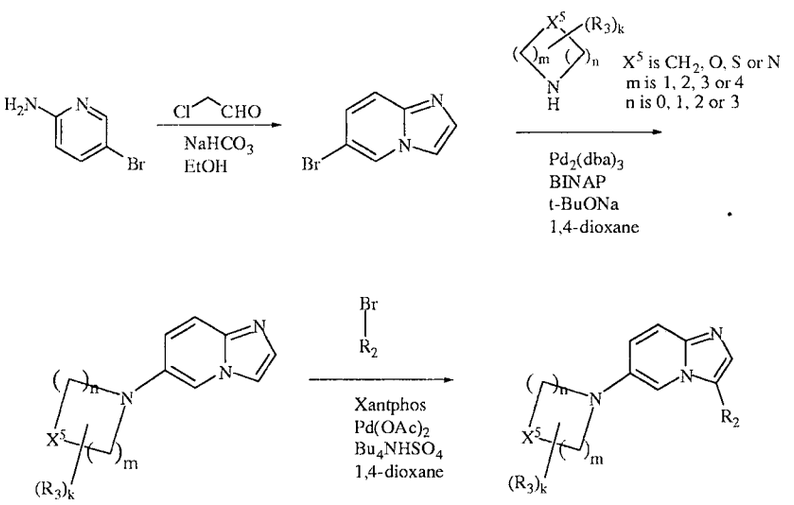
Reaction Scheme (III)



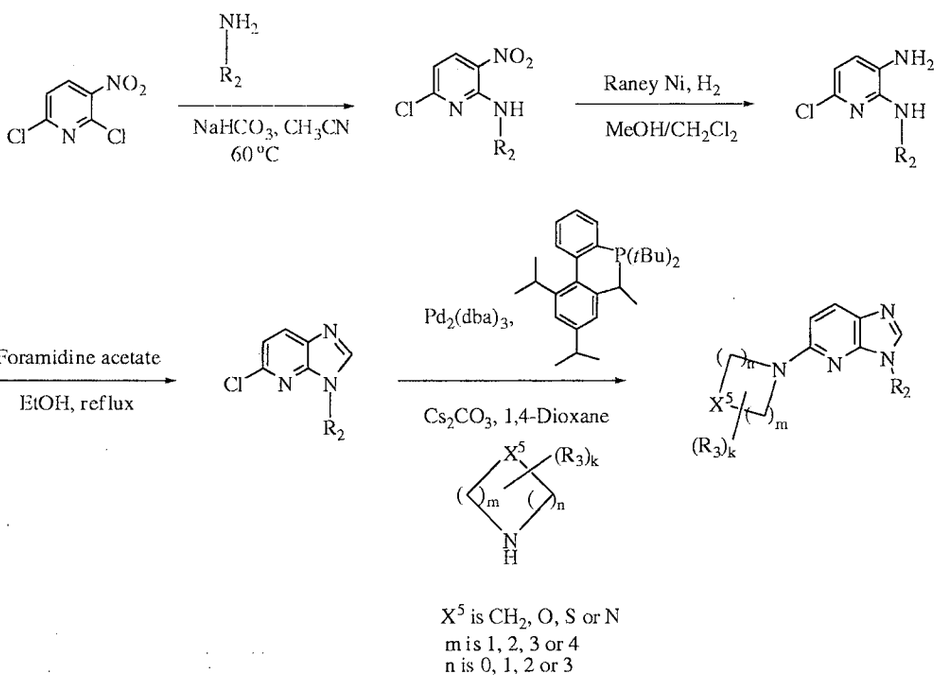
X^5 is CH_2, O, S or N
m is 1, 2, 3 or 4
n is 0, 1, 2 or 3

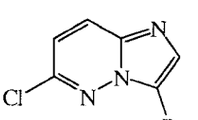
R' is C_1-C_6 alkyl

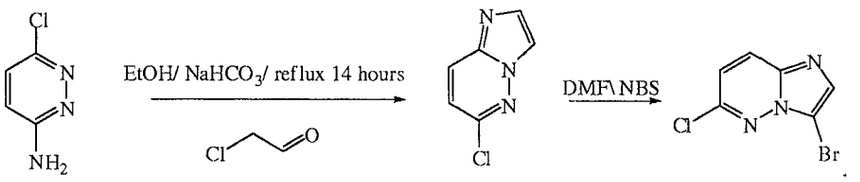
Reaction Scheme (IV)



Reaction Scheme (V)



[000152] A non-limiting example of the synthesis of the intermediate  is shown below:



Pharmacology and Utility

[000153] Protein kinases (PTK) play a central role in the regulation of a wide variety of cellular processes and maintaining control over cellular function. Protein kinases catalyze and regulate the process of phosphorylation, whereby the kinases covalently attach phosphate groups to proteins or lipid targets in response to a variety of extracellular signals. Examples of such stimuli include hormones, neurotransmitters, growth and differentiation factors, cell cycle events, environmental stresses and nutritional stresses. An extracellular stimulus may affect one or more cellular responses related to cell growth, migration, differentiation, secretion of hormones, activation of transcription factors, muscle contraction, glucose metabolism, control of protein synthesis, and regulation of the cell cycle.

[000154] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events. These diseases include, but are not limited to, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, respiratory diseases, allergies and asthma, Alzheimer's disease, and hormone-related diseases.

[000155] Examples of protein-tyrosine kinases include, but are not limited to,

(a) tyrosine kinases such as Irk, IGFR-1, Zap-70, Bmx, Btk, CHK (Csk homologous kinase), CSK (C-terminal Src Kinase), Itk-1, Src (c-Src, Lyn, Fyn, Lck, Syk, Hck, Yes, Blk, Fgr and Frk), Tec, Txk/Rlk, Abl, EGFR (EGFR-1/ErbB-1, ErbB-2/NEU/HER-2, ErbB-3 and ErbB-4), FAK, FGF1R (also FGFR1 or FGR-1), FGF2R (also FGR-2), MET (also Met-I or c-MET), PDGFR (α and β), Tie-1, Tie-2 (also Tek-1 or Tek), VEGFR1 (also FLT-1), c-FMS, VEGFR2 (also KDR), FLT-3, FLT-4, c-KIT, JAK1, JAK2, JAK3, TYK2, LOK, RET, Ros,TRKA, TRKB, TRKC, PYK2, ALK (Anaplastic Lymphoma Kinase), EPHA (1-8), EPHB (1-6), RON, Fes, Fer or EPHB4 (also EPHB4-1), and

(b) and serine/threonine kinases such as Aurora, c-RAF, SGK, MAP kinases (e.g., MKK4, MKK6, etc.), SAPK2α, SAPK2β, Ark, ATM (1-3), CamK (1-IV), CamKK, Chk1 and 2 (Checkpoint kinases), CKI, CK2, Erk, IKK-I (also IKK-ALPHA or CHUK), IKK-2 (also IKK-BETA), Ilk, Jnk (1-3), LimK (1 and 2), MLK3Raf (A, B and C), CDK (1-10), PKC (including all PKC subtypes), Plk (1-3), NIK, Pak (1-3), PDK1, PKR, RhoK, RIP, RIP-2, GSK3 (α and β), PKA, P38, Erk (1-3), PKB (including all PKB subtypes) (also AKT-1, AKT-2, AKT-3 or AKT3-1), IRAK1, FRK, SGK, TAK1 and Tpl-2 (also

COT).

[000156] Phosphorylation modulates or regulates a variety of cellular processes such as proliferation, growth, differentiation, metabolism, apoptosis, motility, transcription, translation and other signaling processes. Aberrant or excessive PTK activity has been observed in many disease states including, but not limited to, benign and malignant proliferative disorders, diseases resulting from inappropriate activation of the immune system and diseases resulting from inappropriate activation of the nervous systems. Specific diseases and disease conditions include, but are not limited to, autoimmune disorders, allograft rejection, graft vs. host disease, diabetic retinopathy, choroidal neovascularization due to age-related macular degeneration, psoriasis, arthritis, osteoarthritis, rheumatoid arthritis, synovial pannus invasion in arthritis, multiple sclerosis, myasthenia gravis, obesity, diabetes mellitus, diabetic angiopathy, retinopathy of prematurity, infantile hemangiomas, non-small cell lung, bladder and head and neck cancers, prostate cancer, breast cancer, ovarian cancer, gastric and pancreatic cancer, psoriasis, fibrosis, rheumatoid arthritis, atherosclerosis, restenosis, auto-immune disease, allergy, respiratory diseases, asthma, transplantation rejection, inflammation, thrombosis, retinal vessel proliferation, inflammatory bowel disease, Crohn's disease, ulcerative colitis, bone diseases, transplant or bone marrow transplant rejection, lupus, chronic pancreatitis, cachexia, septic shock, fibroproliferative and differentiative skin diseases or disorders, central nervous system diseases, neurodegenerative diseases, disorders or conditions related to nerve damage and axon degeneration subsequent to a brain or spinal cord injury, acute or chronic cancer, ocular diseases, viral infections, heart disease, lung or pulmonary diseases or kidney or renal diseases and bronchitis.

[000157] Tyrosine kinases can be broadly classified as receptor-type (having extracellular, transmembrane and intracellular domains) or the non-receptor type (being wholly intracellular) protein tyrosine kinases. Inappropriate or uncontrolled activation of many of these kinase (aberrant protein tyrosine kinase activity), for example by over-expression or mutation, results in uncontrolled cell growth. Many of the protein tyrosine kinases, whether a receptor or non-receptor tyrosine kinase have been found to be involved in cellular signaling pathways involved in numerous pathogenic conditions, including, but not limited to, immunomodulation, inflammation, or proliferative disorders such as cancer.

[000158] Compounds of the invention are screened against a kinase panel (wild type and/or mutation thereof) and modulate the activity of at least one kinase panel member. Examples of kinases that are inhibited by the compounds and pharmaceutical compositions provided herein, and against which the methods described herein are useful, include, but are not limited to Ros, KDR, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, and/or Alk protein kinases, and mutant forms thereof. As such, the compounds and pharmaceutical compositions provided herein are useful for treating diseases or disorders in which such kinases contribute to the pathology and/or symptomology of a disease or disorder associated with such kinases. Such diseases or disorders include, but are not limited to, pancreatic cancer, papillary thyroid carcinoma, ovarian carcinoma, human adenoid cystic carcinoma, non

small cell lung cancer, secretory breast carcinoma, congenital fibrosarcoma, congenital mesoblastic nephroma, acute myelogenous leukemia, psoriasis, metastasis, cancer-related pain and neuroblastoma.

Receptor Tyrosine Kinases (RTKs).

[000159] The Receptor Tyrosine Kinases (RTKs) comprise a large family of transmembrane receptors with diverse biological activities. A number of distinct RTK subfamilies have been identified including, but not limited to, ALK receptor family, EGF receptor family, the Insulin receptor family, the PDGF receptor family, the FGF receptor family, the VEGF receptor family, the HGF receptor family, the Trk receptor family, the EPH receptor family, the AXL receptor family, the LTK receptor family, the TIE receptor family, the ROR receptor family, the DDR receptor family, the RET receptor family, the KLG receptor family, the RYK receptor family and the MuSK receptor family.

[000160] Receptor tyrosine kinases have been shown to be not only key regulators of normal cellular processes but also to have a critical role in the development and progression of many types of cancer. The receptor tyrosine kinase (RTK) family includes receptors that are crucial for the growth and differentiation of a variety of cell types. The intrinsic function of RTK mediated signal transduction is initiated by extracellular interaction with a specific growth factor (ligand), typically followed by receptor dimerization, stimulation of the intrinsic protein tyrosine kinase activity and receptor trans-phosphorylation. Binding sites are thereby created for intracellular signal transduction molecules and lead to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate the appropriate cellular response such as, by way of example only, cell division, differentiation, metabolic effects, and changes in the extracellular microenvironment.

Tropomyosin-Receptor-Kinase (Trk) Family

[000161] The Trk family receptor tyrosine kinases (NTRK genes), TrkA (NTRK1), TrkB (NTRK2), and TrkC (NTRK3), are the signaling receptors that mediate the biological actions of the peptide hormones of the neurotrophin family. Trk receptors are membrane-bound receptors that, through several signal cascades, control neuronal growth and survival, and differentiation, migration and metastasis of tumor cells. The neurotrophin family of growth factors includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and two neurotrophins (NT), NT-3, and NT-4. Neurotrophins are critical to the functioning of the nervous system, and the activation of Trk receptors by neurotrophin binding leads to activation of signal cascades resulting in promoting survival and other functional regulation of cells. Each type of neurotrophin has a different binding affinity toward its corresponding Trk receptor, and upon neurotrophin binding, the Trk receptors phosphorylates themselves and members of the MAPK pathway. The differences in the signaling initiated by these distinct types of receptors are important for generating diverse biological responses.

[000162] The Trk family kinase receptors promote tumorigenesis and are able to control tumor cell growth and survival as well as differentiation, migration and metastasis. The Trk receptors are implicated in

the development and progression of cancer, through upregulation of either, the receptor, their ligand (NGF, BDNF, NT-3, and NT-4), or both. In many cases high Trk expression is associated with aggressive tumor behavior, poor prognosis and metastasis. Thus, diseases and disorders related to Trk receptors result from 1) expression of a Trk receptor(s) in cells which normally do not express such a receptor(s); 2) expression of a Trk receptor(s) by cells which normally do not express such a receptor(s); 3) increased expression of Trk receptor(s) leading to unwanted cell proliferation; 4) increased expression of Trk receptor(s) leading to adhesion independent cell survival; 5) mutations leading to constitutive activation of Trk receptor(s); 6) over stimulation of Trk receptor(s) due to abnormally high amount of, or mutations in, Trk receptor(s), and/or 7) abnormally high amount of Trk receptor(s) activity due to abnormally high amount of, or mutations in, Trk receptor(s).

[000163] Genetic abnormalities, i.e. point mutations and chromosomal rearrangements involving both the genes expressing TrkB and TrkC have been found in a variety of cancer types. In a kinome-wide approach to identify point mutants in tyrosine kinases, mutations in the genes expressing TrkB and TrkC were found in cell lines and primary samples from patients with colorectal cancer. In addition, chromosomal translocations involving the genes expressing TrkA and TrkB have been found in several different types of tumors. Gene rearrangements involving the genes expressing TrkA and a set of different fusion partners (TPM3, TPR, TFG) are a hallmark of a subset of papillary thyroid cancers. Moreover, secretary breast cancer, infant fibrosarcoma and congenital mesoblastic nephroma have been shown to be associated with a chromosomal rearrangement t(12;15) generating a ETV6-NTRK3 fusion gene that was shown to have constitutive kinase activity and transforming potential in several different cell lines including fibroblasts, hematopoietic cells and breast epithelial cells.

[000164] TrkA has the highest affinity to the binding nerve growth factor (NGF). NGF is important in both local and nuclear actions, regulating growth cones, motility, and expression of genes encoding the biosynthesis enzymes for neurotransmitters. Nocireceptive sensory neurons express mostly TrkA and not TrkB or TrkC.

[000165] TrkB serves as a receptor for both BDNF and NT-4, and is expressed in neuroendocrine-type cells in the small intestine and the colon, in the alpha cells of the pancreas, in the monocytes and macrophages of the lymph nodes and of the spleen, and in the granular layers of the epidermis. TrkB is also expressed in cancerous prostate cells but not in normal cells. The binding of BDNF to TrkB receptor causes activation of intercellular cascades which regulate neuronal development and plasticity, long-term potentiation, and apoptosis. BDNF promotes the proliferation, differentiation and growth and survival of normal neural components such as retinal cells and glial cells. In addition, TrkB activation is a potent and specific suppressor of anchorage independent cell death (anoikis), which is apoptosis induced by loss of attachment of a cell to its matrix. By way of example, activation of the Phosphatidylinositol-3--kinase/Protein Kinase B signaling axis by TrkB promotes the survival of non-transformed epithelial cells in

3-dimensional cultures and induces tumor formation and metastasis of those cells in immunocompromised mice. Anchorage independent cell survival is a metastatic process allowing tumor cells to migrate through the systemic circulation and grow at distant organs. Agonism of TrkB results in the failure of induced cell death by cancer treatments. Thus, TrkB modulation is a target for treatment of benign and malignant proliferative diseases, especially tumor diseases.

[000166] Diseases and disorders related to the TrkB receptor include, but are not limited to, cancers, such as, by way of example only, neuroblastoma progression, Wilm's tumor progression, breast cancer, pancreatic cancer, colon cancer, prostate cancer, and lung cancer. The TrkB receptor has been shown to be associated with Alzheimer's disease.

[000167] Additional research has discovered mutations in TrkB in humans that result in a partial loss of enzymatic activity of the receptor. This genetic legion results in an increase in apetite and obesity (hyperphagic obesity). Similar results have been obtained in mouse models, thus strengthening the hypothesis that lowering TrkB activity could serve to modulate feeding behavior, and would be useful in the treatment of disorders such as anorexia.

[000168] Other non-oncology indications for a Trk inhibitor include atopic dermatitis and psoriasis.

[000169] TrkC is activated by binding with NT-3 and is expressed by proprioceptive sensory neurons. The axons of these proprioceptive sensory neurons are much thicker than those of nocireceptive sensory neurons, which express TrkA. Signalling through TrkC leads to cell differentiation and development of proprioceptive neurons that sense body position. Mutations in this gene expressing TrkC is associated with medulloblastomas, secretory breast carcinomas and other cancers. In addition, high expression of TrkC is a hallmark of melanoma, especially in cases with brain metastasis.

[000170] Trk family members, especially NTRK1 and NTRK2, play a role in pancreatic cancer wherein: i) high expression of various members of the Trk family and their cognate ligands have been shown in tissue samples from patients with pancreatic cancer; ii) NTRK2 overexpression has been linked to a malignant, highly metastatic phenotype of pancreatic cancer; iii) high expression of NTRK1/NGF, has been correlated with enhanced proliferation, invasive behavior and pain in PC patients; and iv) nerve growth factor has been shown to increase the invasive potential of pancreatic cancer cell lines. Overexpression of TrkA in pancreatic cancer might be caused by methylation of negative regulatory AP-1 sites in the promoter region of TrkA.

[000171] Gene rearrangements involving NTRK1 are a hallmark of a subset of papillary thyroid cancers. Thyroid-specific *TRK* oncogenes are generated by rearrangements of the *NTRK1* gene with three different activating genes, namely *TPR*, *TPM3*, and *TFG*.

[000172] Several loss of function mutations in thr TrkA are responsible for congenital insensitivity to pain with anhidrosis (CIPA), a disorder characterized by a lack of pain sensation and anhidrosis. More recently, an antagonistic TrkA antibody has been shown to be efficacious in inflammatory and neupathic

pain animal models. In addition, TrkA and NGF have been implicated in eliciting cancer related pain. It was shown that NGF secreted by tumor cell and tumor invading macrophages secret NGF which directly stimulates TrkA located on peripheral pain fibers. Using various tumor models in both mouse and rats it was demonstrated that neutralizing NGF with a monoclonal antibody inhibits cancer related pain to a degree similar or superior to the highest tolerated dose of morphine. Therefore, a selective inhibitor of TrkA can be used in the treatment of pain associated with cancer.

[000173] High expression of Trk's are found in Wilm's tumor, prostate carcinoma and pancreatic cancers. High expression of TrkC is a hallmark of carcinoma. In neuroblastoma, high TRKB expression is correlated with an aggressive untreatable tumors and resistance to standard cytotoxic therapies. In mouse models of cancer metastasis, the NTRK2 gene (TrkB protein) can induce metastasis and removal of the gene reverses this metastatic potential. The bulk of evidence suggests that inhibition of Trk enzymes would block the growth and spread of various cancers where Trk is involved. Furthermore, activating mutations in Trk's are present in 7 % of cancers.

[000174] Certain compounds, pharmaceutical compositions and pharmaceutical combination provided herein are inhibitors of Trk receptor tyrosine kinases (TrkA, TrkB, and TrkC), thus such compounds, pharmaceutical compositions and pharmaceutical combination are useful for the treatment of diseases and/or disorders that respond to inhibition of Trk receptor tyrosine kinases (TrkA, TrkB, and TrkC). In certain embodiments, such compounds, pharmaceutical compositions and pharmaceutical combination are useful in the treatment of cancer by inhibiting the development and/or progression of the cancer. In certain embodiments, such compounds, pharmaceutical compositions and pharmaceutical combination are useful in the treatment of diseases and/or disorders including, but are not limited to, neuroblastoma, Wilm's tumor, breast cancer, pancreatic cancer, colon cancer, prostate cancer, lung cancer, melanoma, anoerexia, atopic dermatitis, psoriasis and Alzheimer's disease.

Platelet-derived Growth Factor (PDGF) receptor family

[000175] PDGF (Platelet-derived Growth Factor) is a very commonly occurring growth factor, which plays an important role both in normal growth and also in pathological cell proliferation, such as is seen in carcinogenesis and in diseases of the smooth-muscle cells of blood vessels, for example in atherosclerosis and thrombosis. The PDGF growth factor family consists of PDGF-A, PDGF-B, PDGF-C and PDGF-D, which form either homo- or heterodimers (AA, AB, BB, CC, DD) that bind to the protein tyrosine kinase receptors PDGFR-α and PDGFR-β. Dimerization of the growth factors is a prerequisite for activation of the kinase, as the monomeric forms are inactive. The two receptor isoforms dimerize upon binding resulting in three possible receptor combinations, PDGFR-$\alpha\alpha$, PDGFR-$\beta\beta$ and PDGFR–$\alpha\beta$. Growth factor AA binds only to -$\alpha\alpha$, growth factor BB can bind with -$\alpha\alpha$, -$\beta\beta$ and -$\alpha\beta$, growth factors CC and AB specifically interact with -$\alpha\alpha$ and -$\alpha\beta$, and growth factor DD binds to -$\beta\beta$.

[000176] Key downstream mediators of PDGFR signaling are Ras/mitogen-activated protein kinase

(MAPK), PI-3 kinase and phospholipase-γ (PLCγ) pathways. MAPK family members regulate various biological functions by phosphorylation of target molecules (transcription factors and other kinases) and thus contribute to regulation of cellular processes such as proliferation, differentiation, apoptosis and immunoresponses. PI-3 kinase activation generated PIP3 which functions as a second messenger to activate downstream tyrosine kinases Btk and Itk, the Ser/Thr kinases PDK1 and Akt (PKB). Akt activation is involved in survival, proliferation and cell growth. After activation PLCγ hydolyses its substrate, PtdIns(4,5)P2, and forms two secondary messengers, diacylglycerol and Ins(1,4,5)P3 which stimulates intracellular processes such as proliferation, angiogenesis and cell motility. The PDGF-receptor plays an important role in the maintenance, growth and development of hematopoietic and non-hematopoietic cells.

[000177] PDGFR is expressed on early stem cells, mast cells, myeloid cells, mesenchymal cells and smooth muscle cells. Only PDGFR-β is implicated in myeloid leukemias-usually as a translocation partner with Tel, Huntingtin interacting protein (HIP1) or Rabaptin5. Activation mutations in PDGFR-α kinase domain are associated with gastrointestinal stromal tumors (GIST).

[000178] Certain compounds, pharmaceutical compositions and pharmaceutical combination provided herein are inhibitors of PDGFR receptor tyrosine kinases, thus such compounds, pharmaceutical compositions and pharmaceutical combination are useful for the treatment of diseases and/or disorders that respond to inhibition of PDGFR receptor tyrosine kinases. In certain embodiments, such compounds, pharmaceutical compositions and pharmaceutical combination are useful in the treatment of hematopoietic and non-hematopoietic cells cancer. In certain embodiments, such compounds, pharmaceutical compositions and pharmaceutical combination are useful in the treatment of diseases and/or disorders including, but are not limited to, myeloid leukemias, and gastrointestinal stromal tumors (GIST).

Vascular Endothelial Growth Factor (VEGF) Receptor family

[000179] VEGF, also known as fms-related tyrosine kinase-1 (FLT1), is an important signaling protein involved in both vasculogenesis (formation of embryonic circulatory system) and angiogenesis (growth of blood vessels from pre-existing vasculature). Structurally VEGF belongs to to the PDGF family of cytokine-knot growth factors. The VEGF sub-family of growth factors includes VEGF-A, VEGF-B, VEGF-C and VEGF-D. VEGF-A binds to receptor VEGFR-1 (Flt-1) and to VEGFR-2 (KDR/Flk-1). VEGF-C and VEGF-D bind to receptor VEGFR-3 and mediate lymphangiogenesis. The VGFR receptors mediate the angiogenic process, and are thus involved in supporting the progression of cancers and other diseases involving inappropriate vascularization (e.g., diabetic retinopathy, choroidal neovascularization due to age-related macular degeneration, psoriasis, arthritis, retinopathy of prematurity, and infantile hemangiomas).

[000180] Certain compounds, pharmaceutical compositions and pharmaceutical combination provided herein are inhibitors of VEGFR-2 (KDR) receptor tyrosine kinases, thus such compounds, pharmaceutical compositions and pharmaceutical combination are useful for the treatment of diseases and/or disorders that

respond to inhibition of VEGFR-2 (KDR) receptor tyrosine kinases. In certain embodiments, such compounds, pharmaceutical compositions and pharmaceutical combination are useful in the treatment of cancer by inhibiting the development and/or progression of the cancer.

Fms-like tyrosine kinase

[000181] The fms-like tyrosine kinase-3 (FLT3) ligand (FLT3L) is one of the cytokines that affects the development of multiple hematopoietic lineages. These effects occur through the binding of FLT3L to the FLT3 receptor, also referred to as fetal liver kinase-2 (flk-2) and STK-1, a receptor tyrosine kinase (RTK) expressed on hematopoietic stem and progenitor cells. FLT3 is a member of the type III receptor tyrosine kinase (RTK) family. The ligand for FLT3 is expressed by the marrow stromal cells and other cells and synergizes with other growth factors to stimulate proliferation of stem cells, progenitor cells, dendritic cells, and natural killer cells. Flt3 plays an important role in the maintenance, growth and development of hematopoietic and non-hematopoietic cells.

[000182] The FLT3 gene encodes a membrane-bound RTK that plays an important role in proliferation, differentiation and apoptosis of cells during normal hematopoiesis. The FLT3 gene is mainly expressed by early myeloid and lymphoid progenitor cells. Hematopoietic disorders are pre-malignant disorders and include, for instance, the myeloproliferative disorders, such as thrombocythemia, essential thrombocytosis (ET), angiogenic myeloid metaplasia, myelofibrosis (MF), myelofibrosis with myeloid metaplasia (MMM), chronic idiopathic myelofibrosis (IMF), and polycythemia vera (PV), the cytopenias, and pre-malignant myelodysplastic syndromes. Hematological malignancies include leukemias, lymphomas (non-Hodgkin's lymphoma), Hodgkin's disease (also called Hodgkin's lymphoma), and myeloma--for instance, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL), anaplastic large-cell lymphoma (ALCL), prolymphocytic leukemia (PML), juvenile myelomonocytic leukemia (JMML), adult T-cell ALL, AML with trilineage myelodysplasia (AML/TMDS), mixed lineage leukemia (MLL), myelodysplastic syndromes (MDSs), myeloproliferative disorders (MPD), multiple myeloma, (MM) and myeloid sarcoma.

[000183] Aberrant expression of the Flt3 gene has been documented in both adult and childhood leukemias including acute myeloid leukemia (AML), AML with trilineage myelodysplasia (AML/TMDS), acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS). Activating mutations of the Flt3 receptor have been found in about 35% of patients with acute myeloblastic leukemia (AML), and are associated with a poor prognosis. The most common mutation involves in-frame duplication within the juxtamembrane domain, with an additional 5-10% of patients having a point mutation at asparagine 835. Both of these mutations are associated with constitutive activation of the tyrosine kinase activity of Flt3, and result in proliferation and viability signals in the absence of ligand. Patients expressing the mutant form of the receptor have been shown to have a decreased chance for cure. Thus, there is accumulating

evidence for a role for hyper-activated (mutated) Flt3 kinase activity in human leukemias and myelodysplastic syndrome.

[000184] FLT-3 and c-Kit regulate maintenance of stem cell/early progenitor pools as well the development of mature lymphoid and myeloid cells. Both receptors contain an intrinsic kinase domain that is activated upon ligand-mediated dimerization of the receptors. Upon activation, the kinase domain induces autophosphorylation of the receptor as well as the phosphorylation of various cytoplasmic proteins that help propagate the activation signal leading to growth, differentiation and survival. Some of the downstream regulators of FLT-3 and c-Kit receptor signaling include, PLCγ, PI3-kinase, Grb-2, SHIP and Src related kinases. Both receptor tyrosine kinases have been shown to play a role in a variety of hematopoietic and non-hematopoietic malignancies. Mutations that induce ligand independent activation of FLT-3 and c-Kit have been implicated acute-myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), mastocytosis and gastrointestinal stromal tumor (GIST). These mutations include single amino acid changes in the kinase domain or internal tandem duplications, point mutations or in-frame deletions of the juxtamembrane region of the receptors. In addition to activating mutations, ligand dependent (autocrine or paracrine) stimulation of over-expressed wild-type FLT-3 or c-Kit can contribute to the malignant phenotype.

[000185] Certain compounds, pharmaceutical compositions and pharmaceutical combination provided herein are inhibitors of FLT-3 receptor tyrosine kinases, thus such compounds, pharmaceutical compositions and pharmaceutical combination are useful for the treatment of diseases and/or disorders that respond to inhibition of FLT-3 receptor tyrosine kinases. In certain embodiments, such compounds, pharmaceutical compositions and pharmaceutical combination are useful in the treatment of hematopoietic disorders. Such hematopoietic disorders include, but are not limited to, the myeloproliferative disorders, such as thrombocythemia, essential thrombocytosis (ET), angiogenic myeloid metaplasia, myelofibrosis (MF), myelofibrosis with myeloid metaplasia (MMM), chronic idiopathic myelofibrosis (IMF), and polycythemia vera (PV), the cytopenias, and pre-malignant myelodysplastic syndromes. Hematological malignancies include leukemias, lymphomas (non-Hodgkin's lymphoma), Hodgkin's disease (also called Hodgkin's lymphoma), and myeloma--for instance, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL), anaplastic large-cell lymphoma (ALCL), prolymphocytic leukemia (PML), juvenile myelomonocytic leukemia (JMML), adult T-cell ALL, AML with trilineage myelodysplasia (AML/TMDS), mixed lineage leukemia (MLL), myelodysplastic syndromes (MDSs), myeloproliferative disorders (MPD), multiple myeloma, (MM) and myeloid sarcoma.

Macrophage Colony-Stimulating Factor Receptor (c-FMS)

[000186] Macrophage colony stimulating factor (M-CSF) is a member of the family of proteins referred

to as colony stimulating factors (CSFs). M-CSF is a secreted cytokine or a cell surface glycoprotein, comprised of two subunits that are joined by a disulfide bond with a total molecular mass varying from 40 to 90 kD. Similar to other CSFs, M-CSF is produced by macrophages, monocytes, and human joint tissue cells, such as chondrocytes and synovial fibroblasts, in response to proteins such as interleukin-1 or tumor necrosis factor-α. M-CSF stimulates the formation of macrophage colonies from pluripotent hematopoietic progenitor stem cells. Eukaryotic cells also produce M-CSF in order to combat intercellular viral infection.

[000187] M-CSF typically bind to its receptor, c-FMS, in order to exert a biological effect. c-FMS contains five extracellular Ig domains, one transmembrane domain, and an intracellular domain with two kinase domains. Upon M-CSF binding to c- FMS, the receptor homo-dimerizes and initiates a cascade of signal transduction pathways including the JAK/STAT, PI3K, and ERK pathways.

[000188] M-CSF is an important regulator of the function, activation, and survival of monocytes/macrophages. M-CSF is involved in various diseases, including rheumatoid arthritis (RA) and cancer. Macrophages comprise key effector cells in RA. The degree of synovial macrophage infiltration in RA has been shown to closely correlate with the extent of underlying joint destruction. M-CSF, endogenously produced in the rheumatoid joint by monocytes/macrophages, fibroblasts, and endothelial cells, acts on cells of the monocyte/macrophage lineage to promote their survival and differentiation into bone destroying osteoclasts, and enhance pro-inflammatory cellular functions such as cytotoxicity, superoxide production, phagocytosis, chemotaxis and secondary cytokine production. For example, treatment with M-CSF in the rat streptococcus agalactiae sonicate-induced experimental arthritis model lead to enhanced pathology. Similarly, subcutaneous injections of M-CSF in a murine model of collagen-induced arthritis, which is a model for RA, results in a significant exacerbation of the RA disease symptoms. Furthermore, MRL/lpr mice that are highly susceptible to RA and other autoimmune diseases have elevated basal M-CSF serum concentrations.

[000189] M-CSF binding to c-FMS and its subsequent activation of monocyte/macrophages is important in a number of disease states. In addition to RA and cancer, the other examples of M-CSF-related disease states include osteoporosis, destructive arthritis, atherogenesis, glomerulonephritis, Kawasaki disease, and HIV-1 infection, in which monocytes/macrophages and related cell types play a role. For instance, osteoclasts are similar to macrophages and are regulated in part by M-CSF. Growth and differentiation signals induced by M-CSF in the initial stages of osteoclast maturation are essential for their subsequent osteoclastic activity in bone. M-CSF is uniquely essential for osteoclastogenesis.

[000190] M-CSF has a central role in atherogenesis, and in proliferative intimal hyperplasia after mechanical trauma to the arterial wall. All the major cell types in atherosclerotic lesions have been shown to express M-CSF, and this is further up-regulated by exposure to oxidized lipoprotein.

[000191] Kawasaki disease (KD) is an acute, febrile, pediatric vasculitis of unknown cause. Its most common and serious complications involve the coronary vasculature in the form of aneurismal dilatation.

Serum M-CSF levels are significantly elevated in acute phase Kawasaki's disease, and normalize following treatment with intravenous immunoglobulin. Giant cell arthritis (GCA) is an inflammatory vasculopathy mainly occurring in the elderly in which T cells and macrophages infiltrate the walls of medium and large arteries leading to clinical consequences that include blindness and stroke secondary to arterial occlusion. The active involvement of macrophages in GCA is evidenced by the presence of elevated levels of macrophage derived inflammatory mediators within vascular lesions.

[000192] M-CSF has been reported to render human monocyte derived macrophages more susceptible to HIV-1 infection in vitro. In a recent study, M-CSF increased the frequency with which monocyte-derived macrophages became infected, the amount of HIV mRNA expressed per infected cell, and the level of proviral DNA expressed per infected culture.

[000193] Certain compounds, pharmaceutical compositions and pharmaceutical combination provided herein are inhibitors of c-FMS receptor tyrosine kinases, thus such compounds, pharmaceutical compositions and pharmaceutical combination are useful for the treatment of diseases and/or disorders that respond to inhibition of c-FMS receptor tyrosine kinases. In certain embodiments, such compounds, pharmaceutical compositions and pharmaceutical combination are useful in the treatment of autoimmune diseases, inflammatory diseases and cancer. In certain embodiments, such compounds, pharmaceutical compositions and pharmaceutical combination are useful in the treatment of diseases and/or disorders includind, but are not limited to, rheumatoid arthritis, ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, skeletal pain caused by tumor metastasis or osteoarthritis, visceral pain, inflammatory pain, neurogenic pain, osteoporosis, Paget's disease, osteoarthritis, prosthesis failure, osteolytic sarcoma, myeloma, tumor metastasis to bone, systemic lupus erythematosus, psoriasis, Sjogren's syndrome, multiple sclerosis, uveitis, atherosclerosis, fibrosis and proliferative vitreoretinopathy.

Insulin-like Growth Factor 1 (IGF-1) Receptor

[000194] The Insulin-like Growth Factor 1 (IGF-1) Receptor is a transmembrane receptor that is activated by IGF-1 and by the related growth factor IGF-2. IGF-1R mediates the effects of IGF-1, which is a polypeptide protein hormone similar in molecular structure to insulin. IGF-1 plays an important role in survival and proliferation in mitosis-competent cells, and growth (hypertrophy) in tissues such as skeletal muscle and cardiac muscle. The IGFR signalling pathway is of critical importance during normal development of mammary gland tissue during pregnancy and lactation. During pregnancy, there is intense proliferation of epithelial cells which form the duct and gland tissue. Following weaning, the cells undergo apoptosis and all the tissue is destroyed. Several growth factors and hormones are involved in this overall process, and IGF-1R is believed to have roles in the differentiation of the cells and a key role in inhibiting apoptosis until weaning is complete.

[000195] The IGF-1R is implicated in several cancers including, but not limited to, breast cancer. In

some instances its anti-apoptotic properties allow cancerous cells to resist the cytotoxic properties of chemotheraputic drugs or radiotherapy. It is further implicated in breast cancer by increasing the metastatic potential of the original tumour by inferring the ability to promote vascularisation.

c–Kit receptor

[000196] The compounds of the present invention also inhibit cellular processes involving stem-cell factor (SCF, also known as the c-kit ligand or steel factor), such as inhibiting SCF receptor (kit) autophosphorylation and SCF-stimulated activation of MAPK kinase (mitogen-activated protein kinase). MO7e cells are a human promegakaryocytic leukemia cell line, which depends on SCF for proliferation.

[000197] c-Kit has a substantial homology to the PDGF receptor and to the CSF-1 receptor (c-Fms). Investigations on various erythroid and myeloid cell lines indicate an expression of the c-Kit gene in early stages of differentiation. Certain tumors such as glioblastoma cells likewise exhibit a pronounced expression of the c-Kit gene.

Anaplastic lymphoma kinase (Ki-1 or ALK)

[000198] Anaplastic lymphoma kinase (ALK) is a 200-kDa receptor tyrosine kinase (RTK) encoded by the *ALK* gene on chromosome 2p23. ALK was first identified as part of the NPM-ALK oncogenic fusion protein in which the N-terminal portion of the phosphoprotein nucleophosmin (NPM) linked to the cytoplasmic portion of ALK. This ocogenic fusion protein results from the (2;5)(p23;q35) translocation that is frequently associated with anaplastic large-cell lymphoma (ALCL). This translocation produces a fusion gene that encodes a soluble chimeric transforming protein comprising the NPM-ALK oncogenic fusion protein. The NPM portion is responsible for the dimerization of the fusion protein, leading to constitutive activation of the kinase and to oncogenicity. ALK is highly homologous to leukocyte tyrosine kinase and belongs to the insulin receptor superfamily of receptor tyrosine kinases. Full-length ALK has the typical structure of an RTK, with a large extracellular domain, a lipophilic transmembrane segment, and a cytoplasmic tyrosine kinase domain. The ALK fusion proteins maintain the intracytoplasmic tail of the ALK receptor at their C terminus. This region contains a catalytic domain, whereas the N-terminal region of all fusion proteins has dimerization domains. As a consequence of dimerization, ALK chimeras undergo autophosphorylation and become constitutively active.

[000199] The *ALK* gene encodes a tyrosine kinase receptor, whose physiologic expression in mammals is largely limited to specific regions of the central and the peripheral nervous system. The normal *ALK* gene is dominantly expressed in the neural system, and the *ALK* mRNA is essentially and transiently expressed in specific regions of the central and peripheral nervous systems, such as the thalamus, mid-brain, olfactory bulb, and peripheral ganglia, and it is mainly localized in neuronal cells. ALK plays an important role in the development of the brain and in the normal development and function of the nervous system by exerting its effects on specific neurons in the nervous system.

[000200] Expression of the ALK protein has also been detected in tumors derived from the nervous

system, such as neuroblastomas. Pleiotrophin (PTN) and midkine, two heparin-binding growth factors with pleiotrophic activities involved in normal development and tumor growth, may serve as possible ligands for ALK in mammals, although it is still unclear whether these molecules are the physiological ligands of ALK.

[000201] Anaplastic lymphoma kinase (ALK) has been implicated in oncogenesis in hematopoietic and non-hematopoietic tumors. The aberrant expression of full-length ALK receptor proteins has been reported in a subset of nonlymphoid tumors, including sarcomas, neuroblastomas, and gliomas and glioblastomas, and ALK fusion proteins have occurred in anaplastic large cell lymphoma (ALCL). Anaplastic large cell lymphomas (ALCLs) represent a subset of non-Hodgkin lymphomas in which the anaplastic lymphoma kinase (ALK) gene is frequently fused to the nucleophosmin (NPM) gene, and is characterized by unique cell morphology and expression of CD30. ALK activity is required for the survival of ALCL cells *in vitro* and *in vivo*. ALK kinase activity is essential for an antiapoptotic effect, as kinase-dead NPM-ALK-expressing cells are not protected against doxorubicin-induced apoptosis. ALK is also involved in different variant chromosomal translocations, all leading to the expression of fusion proteins with a constitutively active kinase.

[000202] Phospholipase C-γ, PI3K, STATs, and Src are important downstream targets of NPM-ALK that contribute to its mitogenic and antiapoptotic activities. Activated ALK chimeras bind multiple adaptor proteins capable of firing different pathways regulating cell proliferation, survival, and transformation. The known adaptors include Grb2, Shc, IRS-1, phospholipase Cγ (PLC-γ) PI3K, and JAK3, which activate numerous downstream molecules, including cyclin D, ERK1/2, STAT, and AKT. The genetic ablation of STAT3 in ALK-positive cells leads to cell death and prevents the generation of B cell neoplasms. PLC-γ and AKT play an essential role in ALK-mediated transformation *in vitro*. Ras/ERK and PLC-γ pathways may contribute to the enhancement of cell growth and Stat3 and PI3K/AKT may play a major role in inhibiting apoptosis.

V-ros UR2 sarcoma virus oncogene homolog 1 (avian), (ROS1 gene)

[000203] The transmembrane tyrosine kinase Ros, encoded by the proto-oncogene *c-ros*, is an orphan tyrosine kinase receptor usually classified as a member of the subfamily of insulin receptors, and is expressed in specific epithelia. The temporal and tissue expression profile of c-Ros in chicken and rats suggests that it plays a role in epithelial cell differentiation during embryogenesis, particularly in the tubules of the kidney and testis. The c-ros oncogene is has been found to be constitutively active in glioblastomas.

[000204] The oncogenic potential of the Ros tyrosine kinase has also been demonstrated by ligand-dependent transformation of NIH3T3 fibroblasts, which were stably transfected with a chimeric receptor consisting of the TrkA/nerve growth factor (NGF) receptor extracellular domain and the Ros transmembrane and cytoplasmic domains. The physiological function of Ros has been characterized in mice with a targeted mutation of *c-ros*. Male $Ros^{-/-}$ mice exhibit defects in differentiation and regionalization of

the epididymal epithelium and, because of this defect, are sterile.

Receptor Serine/Threonine Kinases (RTKs).

Activin-Like Kinase-4 (ALK-4) and Activin-Like Kinase-5 (ALK-5)

[000205] Transforming Growth Factor-β1 (TGF-β1) is the prototypic member of a family of cytokines including the Transforming Growth Factors-β (TGF-βs), activins, inhibins, bone morphogenetic proteins and Mullerian-inhibiting substance, that signal through a family of single transmembrane serine/threonine kinase receptors. These receptors can be divided into two classes, the type I or activin-like kinase receptors and type II receptors. The activin-like kinase receptors are distinguished from the type II receptors in that the activin-like kinase receptors (a) lack the serine/threonine rich intracellular tail, (b) possess serine/threonine kinase domains that are very homologous between type I receptors, and (c) share a common sequence motif called the GS domain, consisting of a region rich in glycine and serine residues. The GS domain is at the amino terminal end of the intracellular kinase domain and is critical for activation by the type II receptor. Several studies have shown that TGF-β signalling requires both the activin-like kinase receptors and type II receptors. Specifically, the type II receptor phosphorylates the GS domain of the type I receptor for TGF-β, activin-like kinase-5 receptor (ALK5), in the presence of TGF-β. The ALK5, in turn, phosphorylates the cytoplasmic proteins smad2 and smad3 at two carboxy terminal serines. The phosphorylated smad proteins translocate into the nucleus and activate genes that contribute to the production of extracellular matrix.

[000206] Activins transduce signals in a manner similar to TGF-β. Activins bind to serine/threonine kinase, the activin type II receptor (ActRIIB), and the activated type II receptor hyper-phosphorylates serine/threonine residues in the GS region of the activin-like kinase-4 receptor (ALK4). The activated ALK4 in turn phosphorylates Smad2 and Smad3. The consequent formation of a hetero-Smad complex with Smad4 results in the activin-induced regulation of gene transcription.

[000207] Activation of the TGF-β1 axis and expansion of extracellular matrix are early and persistent contributors to the development and progression of chronic renal disease and vascular disease. Further, TGF-β1 plays a role in the formation of fibronectin and plasminogen activator inhibitor-1, components of sclerotic deposits, through the action of smad3 phosphorylation by the TGF-β1 receptor ALK5.

[000208] Progressive fibrosis in the kidney and cardiovascular system is a major cause of suffering and death and an important contributor to the cost of health care. TGF-β1 has been implicated in many renal fibrotic disorders. TGF-β1 is elevated in acute and chronic glomerulonephritis, diabetic nephropathy, allograft rejection, HIV nephropathy and angiotensin-induced nephropathy. In these diseases the levels of TGF-β1 expression coincide with the production of extracellular matrix. Three lines of evidence suggest a causal relationship between TGF-β1 and the production of matrix. First, normal glomeruli, mesangial cells and non-renal cells can be induced to produce extracellular-matrix protein and inhibit protease activity by exogenous TGF-β1 in vitro. Second, neutralizing anti-bodies against TGF-β1 can prevent the accumulation

of extracellular matrix in nephritic rats. Third, TGF-β1 transgenic mice or *in vivo* transfection of the TGF-β1 gene into normal rat kidneys resulted in the rapid development of glomerulosclerosis. Thus, inhibition of TGF-β1 activity is indicated as a therapeutic intervention in chronic renal disease.

[000209] TGF-β1 and its receptors are increased in injured blood vessels and are indicated in neointima formation following balloon angioplasty. In addition TGF-β1 is a potent stimulator of smooth muscle cell ("SMC") migration *in vitro* and migration of SMC in the arterial wall is a contributing factor in the pathogenesis of atherosclerosis and restenosis. Moreover, in multivariate analysis of the endothelial cell products against total cholesterol, TGF-β receptor ALK5 correlated with total cholesterol ($P < 0.001$). Furthermore, SMC derived from human atherosclerotic lesions have an increased ALK5/ TGF-β type II receptor ratio. Because TGF-β1 is over-expressed in fibroproliferative vascular lesions, receptor- I variant cells would be allowed to grow in a slow, but uncontrolled fashion, while overproducing extracellular matrix components. TGF-β1 is immunolocalized to non-foamy macrophages in atherosclerotic lesions where active matrix synthesis occurs, suggesting that non-foamy macrophages may participate in modulating matrix gene expression in atherosclerotic remodelling via a TGF-β-dependent mechanism. Therefore, inhibiting the action of TGF-β1 on ALK5 is also indicated in atherosclerosis and restenosis.

[000210] Liver fibrosis is the result of unbalanced wound healing response to chronic liver injury trigged by a number of agents, such as hepatitis B and hepatitis C virus, alcohol or drugs, and autoimmune diseases. Ultimately, liver fibrosis could lead to life-threatening cirrhosis and liver cancer. Several cellular signaling pathways are known to be altered upon chronic liver injury.

TGFβ signaling, its receptors and associated Smad-signaling proteins are well documented to be present in cell types involved in fibrogenesis. The circulating levels of TGFβ have been found to be elevated in a number of animal models of fibrotic diseases including liver fibrosis. Transgenic mice with overexpression of TGFβ1 develop fibrosis in multiple organs including liver, kidney, lungs and heart. Elevated TGFβ signaling is involved in all types of fibrotic diseases including liver fibrosis. TGFβ mediates it signal by binding to two ser/thr kinase receptors, TGFβRII and ALK5. Expressing a dominant negative TGFβRII showed beneficial effects in a rat model of dimethylnitrosamine induced liver fibrosis. Inhibiting TGFβ expression using an antisense approach also reduced liver fibrosis induced by bile duct ligation. Thus, inhibiting TGFβ signaling could be an effective treatment for liver fibrotic diseases.

[000211] TGF-β1 is also indicated in wound repair. Neutralizing antibodies to TGF-β1 have been used in a number of models to illustrate that inhibition of TGF-β1 signalling is beneficial in restoring function after injury by limiting excessive scar formation during the healing process. For example, neutralizing antibodies to TGF-β1 and TGF-β2 reduced scar formation and improved the cytoarchitecture of the neodermis by reducing the number of monocytes and macrophages as well as decreasing dermal fibronectin and collagen deposition in rats. Moreover, TGF-β antibodies also improve healing of corneal wounds in rabbits, and accelerate wound healing of gastric ulcers in the rat. Thus, limiting the activity of TGF-β would be

beneficial in many tissues and any disease with chronic elevation of TGF-β would benefit by inhibiting smad2 and smad3 signalling pathways. TGF-β is also implicated in peritoneal adhesions. Therefore, inhibitors of ALK5 would be beneficial in preventing peritoneal and sub-dermal fibrotic adhesions following surgical procedures. TGF-β is also implicated in photoaging of the skin.

[000212] TGF-β signalling is also implicated in the development of pulmonary disorders, in particular pulmonary hypertension and pulmonary fibrosis. TGF-β1 levels are increased in animal models of pulmonary hypertension. Other studies have suggested that pulmonary endothelial cell-derived TGF-β1 can stimulate the growth of pulmonary vascular smooth muscle cells which may underlie the enhanced muscularisation observed in the pulmonary vasculature of individuals with pulmonary hypertension. Apoptosis of pulmonary microvascular endothelial cells stimulates vascular smooth muscle cell growth. Therefore, inhibiting the action of TGF-β1 on ALK5 is indicated as a therapeutic intervention in pulmonary hypertension.

[000213] Additionally, dys-regulated TGF-β signalling has also been implicated in the development of idiopathic pulmonary fibrosis. Activation of ALK5 results in Smad3-activation and downstream modulation of the expression of genes involved in the fibrotic process such as plasminogen activator inhibitor-1, pro-collagen 3A1, and connective tissue growth factor. The levels of TGF-β1 and its downstream pro-fibrotic mediators have been demonstrated to be up-regulated in bronchoalveolar lavage taken from patients with idiopathic pulmonary fibrosis and in animal models of idiopathic pulmonary fibrosis. Transient over-expression of active TGF-β1 in murine lungs, using adenoviral vector-mediated gene transfer, resulted in progressive pulmonary fibrosis in wild-type mice, whereas no fibrosis was seen in the lungs of Smad3 knockout mice up to 28 days following TGF-β1 challenge. Thus, inhibition of TGF-β1 activation of ALK5 is also indicated for pulmonary fibrosis.

[000214] Activin signalling and overexpression of activin is linked to pathological disorders that involve extracellular matrix accumulation and fibrosis, inflammatory responses, cachexia or wasting, diseases or pathological responses in the central nervous system and hypertension. Studies have shown that TGF- β and activin can act synergistically to induce extracellular matrix production. Activin signalling is also implicated in the development of pulmonary disorders, in particular pulmonary hypertension and pulmonary fibrosis. For example, the expression of activin A in lung samples from patients with interstitial pulmonary fibrosis demonstrated strong expression of activin A on metaplastic epithelium, hyperplastic smooth muscle cells, desquamated cells, and alveolar macrophages. Pulmonary arteries from patients with primary or secondary pulmonary hypertension showed abundant immunoreactive activin A on smooth muscle cells. These findings suggest a potential role for this growth factor, activin A, in the pathogenesis of pulmonary tissue remodelling associated with interstitial pulmonary fibrosis and pulmonary hypertension. An increase in fibroblasts and associated connective tissue is a feature of pulmonary fibrosis and pulmonary hypertension. Activin A has been demonstrated to modulate human lung fibroblast (HFL1) activity,

particularly with respect to proliferation and its differentiation into myofibroblast, thus activin A has potential effects on proliferation of lung fibroblast and its differentiation into myofibroblast, and may contribute to structural remodelling observed in pulmonary fibrosis and hypertension. The induction of pulmonary fibrosis mediated by bleomycin challenge in rats results in the up-regulated expression of activin A in macrophages infiltrated in the lung, and was detected in fibroblasts accumulated in the fibrotic area. Administration of follistatin, an antagonist of activin signalling to bleomycin-treated rats significantly reduced the number of macrophages and neutrophils in bronchoalveolar lavage and reduced the protein content. Follistatin markedly reduced the number of infiltrating cells, ameliorated the destruction of lung architecture, and attenuated lung fibrosis.

[000215] Reduction in TGF-β signalling, through its effector Smad3, enhances the mechanical properties and mineral concentration of the bone matrix, as well as the bone mass, enabling the bone to better resist fracture. Thus, inhibition of TGF-β1 activation of ALK5 is also indicated for increasing mineral density strength and content of bone and may be utilized to treat a wide variety of bone disorders including, but not limited to, osteopenia, osteoporosis, fractures and other disorders in which low bone mineral density are a hallmark of the disease.

[000216] Osteoporosis is a systemic skeletal disorder characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. The osteoporotic syndrome is multi faceted, encompassing primary disorders such as postmenopausal or age-related osteporosis, and secondary conditions that accompany disease states or medications. The mechanical properties and composition of bone matrix, along with bone mass and architecture, are critical determinants of a bone's ability to resist fracture. Thus, in certain embodiments, compounds, pharmaceutical compositions and pharmaceutical combination provided herein are used in preventing or treating bone conditions which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable.

[000217] Diseases or condition mediated by ALK-5 inhibition or ALK-4 inhibition include, but are not limited to, glomerulo-nephritis, diabetic nephropathy, lupus nephritis, hypertension-induced nephropathy, renal interstitial fibrosis, renal fibrosis resulting from complications of drug exposure, HIV-associated nephropathy, transplant necropathy, liver fibrosis due to all etiologies, hepatic dysfunction attributable to infections, alcohol- induced hepatitis, disorders of the biliary tree, pulmonary fibrosis, pulmonary hypertension, acute lung injury, adult respiratory distress syndrome, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, pulmonary disease due to infectious or toxic agents, post-infarction cardiac fibrosis, congestive heart failure, dilated cardiomyopathy, myocarditis, vascular stenosis, restenosis, atherosclerosis, ocular scarring, corneal scarring, proliferative vitreoretinopathy, excessive or hypertrophic scar or keloid formation in the dermis occurring during wound healing resulting from trauma or surgical wounds, peritoneal and sub dermal adhesion, scleroderma, fibrosclerosis, progressive systemic sclerosis,

dermatomyositis, polymyositis, arthritis, ulcers, impaired neurological function, male erectile dysfunction, Alzheimer's disease, Raynaud's syndrome, fibrotic cancers, tumor metastasis growth, radiation-induced fibrosis, thrombosis, and bone conditions such as osteopenia and osteoporosis, which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable.

[000218] Diseases or conditions mediated by ALK-5 inhibition in particular include, but are not limited to, chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, inflammatory or obstructive airways diseases, pulmonary hypertension, ulcers (including diabetic ulcers, chronic ulcers, gastric ulcers, and duodenal ulcers), ocular disorders, corneal wounds, diabetic nephropathy, impaired neuro-logical function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, including, but not limited to kidney fibrosis, lung fibrosis and liver fibrosis, for example, hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-induced hepatitis, haemochromatosis, primary biliary cirrhosis, restenosis, retroperitoneal fibrosis, mesenteric fibrosis, endometriosis, keloids, cancer, abnormal bone function, inflammatory disorders, scarring and photaging of the skin.

[000219] Certain compounds, pharmaceutical compositions and pharmaceutical combination provided herein are inhibitors of ALK-4 receptors, thus such compounds, pharmaceutical compositions and pharmaceutical combination are useful for the treatment of the diseases and/or disorders presented herein that are mediated by with ALK-4 receptors. Certain compounds, pharmaceutical compositions and pharmaceutical combination provided herein are inhibitors of ALK-5 receptors, thus such compounds, pharmaceutical compositions and pharmaceutical combination are useful for the treatment of the diseases and/or disorders presented herein that are mediated by ALK-5 receptors. Certain compounds, pharmaceutical compositions and pharmaceutical combination provided herein are inhibitors of ALK-4 receptors and ALK-5 receptors, thus such compounds, pharmaceutical compositions and pharmaceutical combination are useful for the treatment of the diseases and/or disorders presented herein that are mediated by ALK-4 receptors and ALK-5 receptors.

[000220] In certain embodiments, the compounds, pharmaceutical compositions and pharmaceutical combination provided herein are used to treat and/or prevent inflammatory or obstructive airways diseases including, but not limited to, asthma (both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma), adult/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary or airways disease (COPD or COAD), including chronic bronchitis, or dyspnea associated therewith, acute bronchitis, arachidic bronchitis, catarrhal bronchitis, croupus bronchitis, phthinoid bronchitis, emphysema, pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis,

siderosis, silicosis, tabacosis and byssinosis, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy.

[000221] Prophylactic efficacy in the treatment of asthma is evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. Further evidence is reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant from any previously administered symptomatic asthma therapy.

[000222] In certain embodiments, the compounds, pharmaceutical compositions and pharmaceutical combination provided herein are used to treat and/or prevent pulmonary hypertension including, but not limited to, primary pulmonary hypertension (PPH); secondary pulmonary hypertension (SPH); familial PPH; sporadic PPH; precapillary pulmonary hypertension; pulmonary arterial hypertension (PAH); pulmonary artery hypertension; idiopathic pulmonary hypertension; thrombotic pulmonary arteriopathy (TPA); plexogenic pulmonary arteriopathy; functional classes I to IV pulmonary hypertension; and pulmonary hypertension associated with, related to, or secondary to, left ventricular dysfunction, mitral valvular disease, constrictive pericarditis, aortic stenosis, cardiomyopathy, mediastinal fibrosis, anomalous pulmonary venous drainage, pulmonary venoocclusive disease, collagen vascular disease, congenital heart disease, HIV virus infection, drugs and toxins such as fenfluramines, congenital heart disease, pulmonary venous hypertension, chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorder, chronic exposure to high altitude, neonatal lung disease, alveolar-capillary dysplasia, sickle cell disease, other coagulation disorder, chronic thromboemboli, connective tissue disease, lupus, schistosomiasis, sarcoidosis or pulmonary capillary hemangiomatosis.

[000223] In certain embodiments, the pulmonary hypertension treated with compounds, pharmaceutical compositions and pharmaceutical combination provided herein is pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia, including chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorders, chronic exposure to high altitude, neonatal lung disease and alveolar-capillary dysplasia, but especially chronic obstructive pulmonary disease.

[000224] In certain embodiments, the compounds, pharmaceutical compositions and pharmaceutical combination provided herein are used to treat diseases or disorders mediated by ALK-5 inhibition or ALK-4 inhibition including, but not limited to, pulmonary hypertension, pulmonary fibrosis, liver fibrosis or osteoporosis. In certain embodiments, the compounds, pharmaceutical compositions and pharmaceutical

combination provided herein are used to treat lung fibrosis including, but not limted to, idiopathic pulmonary fibrosis.

[000225] Myostatin, a member of the transforming growth factor β (TGFβ) family, is a key negative regulator of skeletal muscle mass. In double-muscle cattle and in a human body with skeletal muscle hypertrophy, different mutations in the myostatin gene were detected. The important role of myostatin for skeletal muscle growth and disorders was confirmed in a wide variety of *in vivo* and *in vitro* studies. For example, muscle-specific overexpression of myostatin in mice causes loss of muscle mass, whereas myostatin null mice have increased skeletal muscle mass and reduced body fat. In accordance systemic administration of myostatin induces cachexia, whereas inhibition of myostatin by, for example, the myostatin neutralizing antibody JA16 increases muscle mass and strength in wildtype and dystrophic mdx mice. In addition, elevated myostatin levels have been observed in both experimental and clinical muscle atrophies such as in patients with Human Immunodeficiency Virus (HIV), cancer or liver cirrhosis as well as in sarcopenia of old age and under glucocorticoid-treatment. These findings show the high potential of myostatin inhibitors as treatments for muscular atrophies and dystrophies.

[000226] Myostatin signals through Smad2/3, moreover, mature myostatin has been shown to act via activin type IIb and activin receptor like kinase receptors in adipocytes. Myostatin is believed to inhibit differentiation and cause atrophy via activin receptor like kinase receptor signaling. Moreover, inhibition of activin receptor like kinase receptor signaling promotes skMC differentiation and causes skMC hypertrophy.

[000227] The compounds, pharmaceutical compositions and pharmaceutical combination provided herein are also used to treat muscle diseases including muscular atrophies (e.g. disuse), muscular dystrophies (e.g. Duchenne's Muscle Dystrophy, Becker's Muscle Dystrophy, Limb-Girdle Muscle Dystrophy, Facioscapulohumeral Dystrophy), sarcopenia and cachexia.

Aurora Kinase Family

[000228] Aurora kinases are serine/threonine protein kinases that regulate many processes during cell division and are essential for cell proliferation. Aurora kinases play an essential role in the orchestration of chromosome separation and cytokinesis during mitosis. The correct ploidy of cells requires accurate mitotic chromosome separation. Aurora kinase controlls chromatid segregation and helps the dividing cell share its genetic materials with its daughter cells. Defects in this segregation can cause genetic instability, a condition which is highly associated with tumorigenesis. Besides being implicated as mitotic regulators, these three members of the mammalian family have generated significant interest in the cancer research field due to their elevated expression profiles in many human cancers.

[000229] Three Aurora kinases have been identified in mammalian cells: Aurora Kinase A; Aurora Kinase B; and Aurora Kinase C (Aie1). The human Aurora kinases present a similar domain organization, with a N-terminal domain of 39 to 129 residues in length, a protein kinase domain and a short C-terminal

domain containing 15 to 20 residues. All have a highly conserved kinase domain but differ in their N-terminal regions, which vary in length and share low sequence conservation, which determines selectivity during protein-protein interactions. The Aurora kinases have an ATP-binding site with an adjacent cleft which is not present in other kinases.

[000230] The Aurora A (also known as Aurora 2, AIK, BTAK and IAK1) family functions during prophase of mitosis and is required for correct function of the centrosomes (the microtubule organizing centres in eukaryotic cells). Aurora kinase A functions in centosome separation and localizes at the centrosomes, spindle poles and spindle microtubules, in prophase to telophase. Aurora kinase A protein levels and kinase activity are both increased in the late G_2-M phase.Aurora-A kinase is oncogenic and is frequently overexpressed/activated in many human cancer cell lines and tissues, including human ovarian and breast cancers.

[000231] Aurora B (also known as Aurora 1, AIK2, ARK2, and AIM-1) is cell-cycle regulated and plays a role in events that occur during anaphase and/or telophase. Aurora B functions in the attachment of the mitotic spindle to the centromere. Aurora kinase B is a chromosomal passenger protein localizing first to centromeres and then to the midzone of mitotic cells during telophase. Histone H3 phosphorylation is important for chromosome condensation and entry into mitosis. Phosphorylaation of histone H3 is controlled by Aurora A and Aurora B.

[000232] Aurora C (Mouse Aie1 and human AIE2, also known as STK-13, and AIK3 AURKC) exhibit a testis-specific expression pattern. Aurora-C kinase may, like Aurora-B kinase, function as a chromosomal passenger protein localizing first to centromeres and then to the midzone of mitotic cells. Aurora-C was first detected at clusters of chromocenters in diplotene spermatocytes and was concentrated at centromeres in metaphase I and II. Interestingly, Aurora-C was also found along the chromosome axes, including both the regions of centromeres and the chromosome arms in diakinesis. During the anaphase I/telophase I and anaphase II/telophase II transitions, Aurora-C was relocalized to the spindle midzone and midbody. The level of Aurora-C transcript is elevated in several human cancer cell types.

Non-Receptor Tyrosine Kinases.

[000233] Non-receptor tyrosine kinases represent a collection of cellular enzymes that lack extracellular and transmembrane sequences. Over twenty-four individual non-receptor tyrosine kinases, comprising eleven (11) subfamilies (Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack and LIMK) have been identified. The Src subfamily of non-receptor tyrosine kinases is comprised of the largest number of PTKs and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk. The Src subfamily of enzymes has been linked to oncogenesis and immune responses.

[000234] The Src family of kinases is implicated in cancer, immune system dysfunction osteopetrosis, and bone remodeling diseases, and therefore Src kinases are considered as potential therapeutic targets for various human diseases. Src expression is linked to cancers such as colon, breast, hepatic and pancreatic

cancer, certain B-cell leukemias and lymphomas. In addition, antisense Src expressed in ovarian and colon tumor cells inhibits tumor growth.

[000235] Csk, or C-terminal Src kinase, phosphorylates and thereby inhibits Src catalytic activity. Suppression of arthritic bone destruction has been achieved by the overexpression of Csk in rheumatoid synoviocytes and osteoclasts. This implies that Src inhibition may prevent joint destruction that is characteristic in patients suffering from rheumatoid arthritis. Src also plays a role in the replication of hepatitis B virus. The virally encoded transcription factor HBx activates Src in a step required for propagation of the virus.

[000236] Other Src family kinases are also potential therapeutic targets. Lck plays a role in T-cell signaling, and mice that lack the Lck gene have a poor ability to develop thymocytes. The function of Lck as a positive activator of T-cell signaling suggests that Lck inhibitors may be useful for treating autoimmune disease such as rheumatoid arthritis. Hck, Fgr and Lyn are important mediators of integrin signaling in myeloid leukocytes. Inhibition of these kinase mediators may therefore be useful for treating inflammation.

Janus Kinase Family (JAK)

[000237] Janus kinase (JAK) is a family of intracellular non-receptor tyrosine kinases, ranging from 120-140 kDa in size that transduce cytokine-mediated signals via the JAK-STAT pathway. The JAK family includes four members: JAK1, JAK2, JAK3 and TYK2. Type I and type II cytokine receptor families possess no catalytic kinase activity, and therefore rely on the JAK family of tyrosine kinases to phosphorylate and activate downstream proteins involved in their signal transduction pathways.

[000238] The receptors exist as paired polypeptides thus exhibiting two intracellular signal-transducing domains. JAKs possess two near-identical phosphate-transferring domains, with one domain exhibiting the kinase activity while the other plays a role in downstream signaling. JAKs associate with a proline-rich region in each intracellular domain, which is adjacent to the cell membrane and called a box1/box2 region. After the receptor associates with its respective cytokine/ligand it goes through a conformational change, bringing the two JAKs close enough to phosphorylate each other. The JAK autophosphorylation induces a conformational change within itself enabling it to transduce the intracellular signal by further phosphorylating and activating transcription factors called STATs. The activated STATs dissociate from the receptor and form dimers before translocating to the cell nucleus where they regulate transcription of selected genes.

[000239] JAK1 is essential for signaling for certain type I and type II cytokines. It interacts with the common gamma chain (γc) of type I cytokine receptors, to elicit signals from the IL-2 receptor family (e.g. IL-2R, IL-7R, IL-9R and IL-15R), the IL-4 receptor family (e.g. IL-4R and IL-13R), the gp130 receptor family (e.g. IL-6R, IL-11R, LIF-R, OSM-R, cardiotrophin-1 receptor (CT-1R), ciliary neurotrophic factor receptor (CNTF-R), neurotrophin-1 receptor (NNT-1R) and Leptin-R). JAK1 is also important for

transducing a signal by type I (IFN-α/β) and type II (IFN-γ) interferons, and members of the IL-10 family via type II cytokine receptors. JAK1 plays a critical role in initiating responses to multiple major cytokine receptor families.

[000240] JAK2 has been implicated in signaling by members of the type II cytokine receptor family (e.g. interferon receptors), the GM-CSF receptor family (IL-3R, IL-5R and GM-CSF-R), the gp130 receptor family (e.g IL-6R), and the single chain receptors (e.g. Epo-R, Tpo-R, GH-R, PRL-R). JAK2 signaling is activated downstream from the prolactin receptor. JAK2 gene fusions with the TEL(ETV6) (TEL-JAK2) and PCM1 genes have been found in leukemia patients. Further, mutations in JAK2 have been implicated in polycythemia vera, essential thrombocythemia, and other myeloproliferative disorders. This mutation, a change of valine to phenylalanine at the 617 position, appears to render hematopoietic cells more sensitive to growth factors such as erythropoietin and thrombopoietin.

[000241] JAK3 functions in signal transduction and interacts with members of the STAT (signal transduction and activators of transcription) family. JAK3 is predominantly expressed in immune cells and transduces a signal in response to its activation via tyrosine phosphorylation by interleukin receptors. Mutations that abrogate JAK3 function cause an autosomal SCID (severe combined immunodeficiency disease). JAK3 expression is restricted mostly to hematopoietic cells. It is most commonly expressed in T cells and NK cells, but has been induced in other leukocytes, including monocytes. JAK3 is involved in signal transduction by receptors that employ the common gamma chain (γC) of the type I cytokine receptor family (e.g. IL-2R, IL-4R, IL-7R, IL-9R, IL-15R, and IL-21R) [2]. Mutations of JAK3 result in severe combined immunodeficiency (SCID).

[000242] Tyrosine kinase 2 (TYK2) is implicated in IFN-α, IL-6, IL-10 and IL-12 signaling.

Leukocyte-Specific Protein Tyrosine Kinase (Lck)

[000243] Lck (or leukocyte-specific protein tyrosine kinase) is a protein located in lymphocytes. Lck is a member of the Src family of tyrosine kinases and it phosphorylates tyrosine residues of certain proteins involved in the intracellular signaling pathways of lymphocytes.

[000244] Lck is most commonly found in T cells. It associates with the cytoplasmic tails of the CD4 and CD8 co-receptors on T helper cells and cytotoxic T cells, respectively, to assist signaling from the T cell receptor (TCR) complex. When the T cell receptor is engaged by the specific antigen presented by MHC, Lck acts to phosphorylate the intracellular chains of the CD3 and ζ-chains of the TCR complex, allowing another cytoplasmic tyrosine kinase called ZAP-70 to bind to them. Lck then phosphorylates and activates ZAP-70, which in turn phosphorylates another molecule in the signaling cascade called LAT (short for Linker of Activated T cells), a transmembrane protein that serves as a docking site for a number of other proteins, the most important of which are Shc-Grb2-SOS, PI3K, and phospholipase C (PLC).

[000245] The tyrosine phosphorylation cascade initiated by Lck culminates in the intracellular mobilization of a calcium (Ca2+) ions and activation of important signaling cascades within the

lymphocyte. These include the Ras-MEK-ERK pathway, which goes on to activate certain transcription factors such as NFAT, NFκB, and AP-1. These transcription factors regulate the production of a large number of gene products, most notable, cytokines such as Interleukin-2 that promote long-term proliferation and differentiation of the activated lymphocytes.

[000246] Lck tyrosine phosphorylates a number of proteins, the most important of which are the CD3 receptor, ZAP-70, SLP-76, the IL-2 receptor, Protein kinase C, ITK, PLC, SHC, RasGAP, Cbl, Vav1, and PI3K.

Lipid Kinases.

PI3-kinase(PIKK)

[000247] The phosphatidylinositol-3'-OH kinase (PI3K) pathway is one of the central signaling pathways that exerts its effect on numerous cellular functions including cell cycle progression, proliferation, motility, metabolism and survival. An activation of receptor tyrosine kinases causes PI3K to phosphorylate phosphatidylinositol-(4,5)-diphosphate, resulting in membrane-bound phosphatidylinositol-(3,4,5)-triphosphate. The latter promotes the transfer of a variety of protein kinases from the cytoplasm to the plasma membrane by binding of phosphatidylinositol-(3,4,5)-triphosphate to the pleckstrin-homology (PH) domain of the kinase. Kinases that are key downstream targets of PI3K include phosphoinositide-dependent kinase 1 (PDK1) and AKT (also known as Protein Kinase B). Phosphorylation of such kinases then allows for the activation or deactivation of numerous other pathways, involving mediators such as GSK3, mTOR, PRAS40, FKHD, NF-κB, BAD, Caspase-9, and the like. An important negative feedback mechanism for the PI3K pathway is PTEN, a phosphatase that catalyses the dephosphorylation of phosphatidylinositol-(3,4,5)-triphosphate to phosphorylate phosphatidylinositol-(4,5)-diphosphate. In more than 60 % of all solid tumors, PTEN is mutated into an inactive form, permitting a constitutive activation of the PI3K pathway. As most cancers are solid tumors, such an observation provides evidence that a targeting of PI3k itself or individual downstream kinases in the PI3K pathway provide a promising approach to mitigate or even abolish the dysregulation in many cancers and thus restore normal cell function and behaviour. This, however, does not exclude that other mechanisms may be responsible for the beneficial effects of PI3K activity modifying agents such as those compounds provided herein.

[000248] In certain embodiments, the compounds and pharmaceutically acceptable salts and solvates thereof, provided herein and inhibit the activity of the lipid kinases, such as the PI3-kinase and/or members of the PI3-kinase-related protein kinase family (also called PIKK and include DNA-PK, ATM, ATR, hSMG-1 and mTOR), such as the DNA protein-kinase. Such compounds and pharmaceutically acceptable salts and solvates thereof, are useful in the treatment of conditions which are mediated by the activation (including normal activity or especially overactivity) of one or more of the members of the PI3 kinase family, especially PI3 kinase enzyme, such as proliferative, inflammatory or allergic conditions, obstructive airways diseases and/or disorders commonly occurring in connection with transplantation.

[000249] In accordance with the foregoing, the present invention further provides a method for preventing or treating any of the diseases or disorders described above in a subject in need of such treatment, which method comprises administering to said subject a therapeutically effective amount (*See, "Administration and Pharmaceutical Compositions", infra*) of a compound of Formula I or a pharmaceutically acceptable salt thereof. For any of the above uses, the required dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired.

Routes of Administration and Pharmaceutical Compositions

[000250] 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 routes of administration of compounds of Formula (I) and pharmaceutical compositions include, but are not limited to, oral administration, intravitreal administration, rectal administration, parenteral, intravenous administration, intraperitoneal administration, intramuscular administration, inhalation, transmucosal administration, pulmonary administration, intestinal administration, subcutaneous administration, intramedullary administration, intrathecal administration, direct intraventricular, intranasal administration, topical administration, ophthalmic administration or otic administration.

[000251] In certain embodiments, compounds of Formula (I) or pharmaceutical compositions described herein are administered locally, while in other embodiments compounds of Formula (I) or pharmaceutical composite described herein are administered systemically. Local administration includes, but is not limited to, injection into an organ, optionally in a depot or sustained release formulation. Systemic administration includes, but is not limited to, oral administration or intravenous administration. In other embodiments, compounds of Formula (I) or pharmaceutical compositions described herein are administered in a targeted drug delivery system, such as, by way of example only, in a liposome coated with organ-specific antibody. The liposome is targeted to and taken up selectively by the organ. In other embodiments, compounds of Formula (I) or pharmaceutical compositions described herein are administered in the form of a rapid release formulation, while in other embodiments, compounds of Formula (I) or pharmaceutical compositions described herein are administered in the form of an extended release formulation . In other embodiments, compounds of Formula (I) or pharmaceutical compositions described herein are administered in the form of an intermediate release formulation.

[000252] 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 route of administration and the treatment desired. In certain embodiments, satisfactory results are indicated to be obtained at daily dosages daily dosage of a compound of Formula (I) from about 0.03 to 2.5mg/kg per body weight. In certain embodiments, the daily dosage of a compound of Formula (I), administered orally, is in the range from 0.05 micrograms per kilogram body weight (μg/kg) to 100 micrograms per kilogram body weight (μg/kg). In certain embodiments, the daily dosage of a compound of Formula (I), administered topically, 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 parenterally, is in the range from 0.05 micrograms per kilogram body weight (μg/kg) to 100 milligrams per kilogram body weight (mg/kg). In certain embodiments, the daily dosage of a compound of Formula (I), administered intrermuscularlly, is in the range from 0.05 micrograms per kilogram body weight (μg/kg) to 100 micrograms per kilogram body weight (μg/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).

[000253] Other aspects provided herein are processes for the preparation of pharmaceutical composition which comprise at least one compound of Formula (I) described herein. In certain embodiments, such processes include admixing a compound of Formula (I) described herein with one or more pharmaceutically acceptable carriers, diluents or excipients. In certain embodiments, the pharmaceutical compositions comprise a compound of Formula (I) in free form or in a pharmaceutically acceptable salt or solvate form. 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, dissolving, granulating dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes 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

[000254] 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, pills, dragees, granules, liquids, gels, syrups, flavored syrups, elixirs, slurries, 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. 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.

[000255] 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.

[000256] 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.

[000257] 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.

[000258] 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.

[000259] Non-limiting examples of such diluents include, but are not limited to, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycine or combinations thereof.

[000260] 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.

[000261] 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.

[000262] Administration of compound 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

[000263] 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.

[000264] 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, physiological saline buffer, Ringer's Injection solution, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection solution; 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.

[000265] In certain embodiments, a compound of Formula (I) or composition containing one or more

compounds of Formula (I) is parenteral administration by bolus injection. In other embodiments, a compound of Formula (I) or composition containing one or more compounds of Formula (I) is parenteral administration by continuous infusion. Formulations for injection are presented in unit dosage form, by way of example only, in ampoules or formulations for injection are presented in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Transdermal Administration

[000266] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) are administered transdermally. 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. In certain embodiments transdermal administration is used to provide continuous, while in other embodiments transdermal administration is used to provide discontinuous infusion of a compound of Formula (I) in controlled amounts.

[000267] In certain embodiments, the rate of absorption is slowed by using rate-controlling membranes or by trapping the compound within a polymer matrix or gel. In certain embodiments, transdermal delivery is via a transdermal patch.

[000268] 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.

[000269] In certain embodiments, such transdermal delivery systems include penetration enhancers to assist in delivering one or more compound 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 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 compound 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 compound of Formula (I) are used to further adjust the properties of the resulting composition.

[000271] In other embodiments, transdermal delivery of the compound of Formula (I) is accomplished by means of iontophoretic patches and the like

Topical Dosage Forms

[000272] 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.

[000273] 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.

[000274] In certain embodiments, such topical formulations include penetration enhancers to assist in delivering one or more compound 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).

Pulmonary Administration

[000275] 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.

[000276] In certain embodiments, compound 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, compound 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, compound 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, compound 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.

[000277] 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.

[000278] 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.

Rectal Administration

[000279] In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) are administered rectally in the form of suppositories, enemas, retention 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.

Depot Administration

[000280] 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.

[000281] In certain embodiments injectable depot forms are made by forming microencapsulated matrices of the compound of Formula (I) in biodegradable polymers. The rate of compound of Formula (I) release is controlled by varying the ratio of compound of Formula (I) to polymer and the nature of the

particular polymer employed. In other embodiments, depot injectable formulations are prepared by entrapping the compound of Formula (I) in liposomes or microemulsions.

Ophthalmic Administration

[000282] In certain embodiments, a compound of Formula (I) or pharmaceutical composition described herein are ophthalmically administered to the eye. Administration to the eye generally results in direct contact of the agents with the cornea, through which at least a portion of the administered agents pass. In certain embodiments, such compounds of Formula (I) or pharmaceutical compositions have an effective residence time in the eye of about 2 to about 24 hours. In certain embodiments, such compounds of Formula (I) or pharmaceutical compositions have an effective residence time in the eye of about 4 to about 24 hours. In certain embodiments, such compounds of Formula (I) or pharmaceutical compositions have an effective residence time in the eye of about 6 to about 24 hours.

[000283] Ophthalmic administration, as used herein, includes, but is not limited to, topical administration, intraocular injection, subretinal injection, intravitreal injection, periocular administration, subconjuctival injections, retrobulbar injections, intracameral injections (including into the anterior or vitreous chamber), sub-Tenon's injections or implants, ophthalmic solutions, ophthalmic suspensions, ophthalmic ointments, ocular implants and ocular inserts, intraocular solutions, use of iontophoresis, incorporation in surgical irrigating solutions, and packs (by way of example only, a saturated cotton pledget inserted in the fornix). In certain embodiments, the compounds of Formula (I) or pharmaceutical composition described herein are formulated as an ophthalmic composition and are administered topically to the eye. Such topically administered ophthalmic compositions include, but are not limited to, solutions, suspensions, gels or ointments.

[000284] In certain embodiments the pharmaceutical compositions, comprising at least one compound of Formula (I) described herein, used for ophthalmic administration take the form of a liquid where the compositions are present in solution, in suspension or both. In some embodiments, a liquid composition includes a gel formulation. In other embodiments, the liquid composition is aqueous. In other embodiments, such liquid compositions take the form of an ointment. In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) are administered ophthamically as eye drops formulated as aqueous solutions that optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives. A desired dosage is administered via a known number of drops into the eye. By way of example only, for a drop volume of 25 µl, administration of 1-6 drops delivers 25-150 µl of the composition. In certain embodiments, the aqueous compositions contain from about 0.01% to about 50% weight/volume of a compound of Formula (I). In other embodiments, the aqueous compositions contain from about 0.1% to about 20% weight/volume of a compound of Formula (I). In still other embodiments, the aqueous compositions contain from about 0.2% to about 10% weight/volume of a compound of Formula (I). In certain embodiments, the aqueous compositions contain from about 0.5% to about 5%,

weight/volume of a compound of Formula (I).

[000285] In certain embodiments the aqueous compositions have an ophthalmically acceptable pH and osmolality. In certain embodiments the aqueous compositions include one or more ophthalmically acceptable pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an ophthalmically acceptable range.

[000286] In certain embodiments the compositions also include also include one or more ophthalmically acceptable salts in an amount required to bring osmolality of the composition into an ophthalmically acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

[000287] In certain embodiments the aqueous compositions also contain one or more polymers as suspending agents. Such polymers include, but are not limited to, water-soluble polymers such as cellulosic polymers described herein, (for example only, hydroxypropyl methylcellulose), and water-insoluble polymers described herein (for example only, cross-linked carboxyl-containing polymers). In certain embodiments, the aqueous compositions also include an ophthalmically acceptable mucoadhesive polymer, selected for example from carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

[000288] In certain embodiments the compositions also include ophthalmically acceptable solubilizing agents to aid in the solubility of a compound of Formula (I). The term "solubilizing agent" generally includes agents that result in formation of a micellar solution or a true solution of the agent. In certain embodiments, ophthalmically acceptable nonionic surfactants including, but not limited to, polysorbate 80 are used as solubilizing agents. In other embodiments, ophthalmically acceptable glycols including, but not limited to, polyglycols, polyethylene glycol 400, and glycol ethers are used as solubilizing agents.

[000289] In certain embodiments the compositions also include one or more ophthalmically acceptable surfactants to enhance physical stability or for other purposes. Such nonionic surfactants include, but are not limited to, polyoxyethylene fatty acid glycerides and vegetable oils (by way of example only, polyoxyethylene (60) hydrogenated castor oil) and polyoxyethylene alkylethers and alkylphenyl ethers (by way of example only, octoxynol 10 and octoxynol 40).

[000290] In certain embodiments the compositions also include one or more ophthalmically acceptable preservatives to inhibit microbial activity. Such preservatives include, but are not limited to mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary

ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

[000291] In certain embodiments the compositions also include one or more antioxidants to enhance chemical stability where required. Such antioxidants include, but are not limited to, ascorbic acid and sodium metabisulfite.

[000292] In certain embodiments, the aqueous compositions provided herein are packaged in single-dose non-reclosable containers, while in other embodiments the aqueous compositions provided herein are packaged in multiple-dose reclosable containers wherein a preservative is included in the composition.

Otic Administration

[000293] 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. Combination Therapies

[000294] In certain embodiments, a compound of Formula (I) provided herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I), is administered alone (without an additional therapeutic agent) for the treatment of one or more of the disease and/or disorders associated with Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK protein kinase activity described herein.

[000295] In certain embodiments, a compound of Formula (I) provided herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I), is administered alone (without an additional therapeutic agent) for the treatment of one or more of the disease and/or disorders associated with TrkA, TrkB, TrkC, IGF-1R, and/or ALK protein kinase activity described herein.

[000296] In other embodiments, a compound of Formula (I) provided herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I) provided 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 Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK protein kinase activity described herein.

[000297] In other embodiments, a compound of Formula (I) provided herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I) provided 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 TrkA, TrkB, TrkC, IGF-1R and/or ALK protein kinase activity described herein.

[000298] In other embodiments, a compound of Formula (I) provided herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I) provided 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 Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK protein kinase activity described herein.

[000299] In other embodiments, a compound of Formula (I) provided herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I) provided 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 TrkA, TrkB, TrkC, IGF-1R and/or ALK protein kinase activity described herein.

[000300] In another embodiment, a compound of Formula (I) provided herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I) provided 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 Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK protein kinase activity described herein.

[000301] In another embodiment, a compound of Formula (I) provided herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing at least one compound of Formula (I) provided 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 TrkA, TrkB, TrkC, IGF-1R and/or ALK protein kinase activity described herein.

[000302] In other embodiments, the combination treatments provided herein include administration of a compound of Formula (I) provided herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing a compound of Formula (I) 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 with Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK protein kinase activity described herein.

[000303] In other embodiments, the combination treatments provided herein include administration of a compound of Formula (I) provided herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing a compound of Formula (I) 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 with TrkA, TrkB, TrkC, IGF-1R and/or ALK protein kinase activity described herein.

[000304] In other embodiments, the combination treatments provided herein include administration of a compound of Formula (I) provided herein, or a pharmaceutically acceptable salt or solvate thereof, or a

pharmaceutical composition containing a compound of Formula (I), 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 Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK protein kinase activity described herein.

[000305] In other embodiments, the combination treatments provided herein include administration of a compound of Formula (I) provided herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing a compound of Formula (I), 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 TrkA, TrkB, TrkC, IGF-1R and/or ALK protein kinase activity described herein.

[000306] In other embodiments, the combination treatments provided herein include administration of a compound of Formula (I) provided herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing a compound of Formula (I), concurrently with administration of one or more additional therapeutic agents, for the treatment of one or more of the disease and/or disorders associated with Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK protein kinase activity described herein.

[000307] In other embodiments, the combination treatments provided herein include administration of a compound of Formula (I) provided herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing a compound of Formula (I), concurrently with administration of one or more additional therapeutic agents, for the treatment of one or more of the disease and/or disorders associated with TrkA, TrkB, TrkC, IGF-1R and/or ALK protein kinase activity described herein.

[000308] In certain embodiments, the combination treatments provided herein include administration of a compound of Formula (I) provided herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing a compound of Formula (I)-(XIX) formulated with one or more additional therapeutic agents, for the treatment of one or more of the disease and/or disorders associated with Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK protein kinase activity described herein.

[000309] In certain embodiments, the combination treatments provided herein include administration of a compound of Formula (I) provided herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing a compound of Formula (I)-(XIX) formulated with one or more additional therapeutic agents, for the treatment of one or more of the disease and/or disorders associated with TrkA, TrkB, TrkC, IGF-1R and/or ALK protein kinase activity described herein.

[000310] 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 Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK protein kinase activity. In certain embodiments of the combination treatments described herein

the compounds of Formula (I), or a pharmaceutically acceptable salts or solvates thereof, are inhibitors of TrkA, TrkB, TrkC, IGF-1R and/or ALK protein kinase activity.

[000311] In certain embodiments of the combination therapies described herein, the compounds of Formula (I) provided 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) provided herein, or a pharmaceutically acceptable salts or solvates thereof, and the additional therapeutics agent(s) act synergistically.

[000312] In other embodiments, a compound of Formula (I) provided 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.

[000313] The additional therapeutic agents used in combination with at least one compound of Formula (I) provided herein, or a pharmaceutically acceptable salt or solvate thereof, include, but are not limited to chemotherapeutic agents, anti-inflammatory agents, bronchodilatory agents, antihistamine agents, decongestant agents, anti-tussive agents, immunomodulatory agents antiproliferative agents, cytostatic agents, cytotoxic agents,

inhibitors of polyamine biosynthesis, inhibitors of a protein kinase, inhibitors of a serine/threonine protein kinase, inhibitors of protein kinase C, inhibitors of a tyrosine protein kinase, inhibitors of EGF receptor tyrosine kinase, (e.g. Iressa®,

inhibitors of VEGF receptor tyrosine kinase, (e.g. PTK787 or Avastin®), inhibitors of PDGF receptor tyrosine kinase, (e.g. STI571 (Glivec®)), a cytokine, a negative growth regulator, such as TGF-ß or IFN-ß, an aromatase inhibitor (e.g. letrozole (Femara®) or anastrozole), an inhibitor of the interaction of an SH2 domain with a phosphorylated protein, antiestrogens, bisphosphonates (e.g. AREDIA® or ZOMETA®) and monoclonal antibodies (e.g. against HER2, such as trastuzumab).

[000314] 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, budesonide, ciclesonide,

clobetasol proprionate, clocortolone pivalate, hydrocortisone, hydrocortisone derivatives, desonide, desoximatasone, dexamethasone, flunisolide, flucoxinolide, flurandrenolide, fluticasone propionate, glucocorticosteroids, 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.

[000315] Other 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, steroids described in WO 02/88167, WO 02/12266, WO 02/100879, WO 02/00679 (especially those of Examples 3, 11, 14, 17, 19, 26, 34, 37, 39, 51, 60, 67, 72, 73, 90, 99 and 101), WO 03/35668, WO 03/48181, WO 03/62259, WO 03/64445, WO 03/72592, WO 04/39827 and WO 04/66920; non-steroidal glucocorticoid receptor agonists, such as those described in DE 10261874, WO 00/00531, WO 02/10143, WO 03/82280, WO 03/82787, WO 03/86294, WO 03/104195, WO 03/101932, WO 04/05229, WO 04/18429, WO 04/19935, WO 04/26248 and WO 05/05452; LTB4 antagonists such as BIIL 284, CP-195543, DPC11870, LTB4 ethanolamide, LY 293111, LY 255283, CGS025019C, CP-195543, ONO-4057, SB 209247, SC-53228 and those described in US 5451700 and WO 04/108720; LTD4 antagonists such as montelukast, pranlukast, zafirlukast, accolate, SR2640, Wy-48,252, ICI 198615, MK-571, LY-171883, Ro 24-5913 and L-648051; dopamine receptor agonists such as cabergoline, bromocriptine, ropinirole and 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy)-propyl]sulfonyl]ethyl]amino]ethyl]-2(3H)-benzothiazolone and pharmaceutically acceptable salts thereof (the hydrochloride being Viozan® - AstraZeneca); PDE4 inhibitors such as cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 / PD168787 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene), SelCID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo), GRC 3886 (Oglemilast, Glenmark), WO 92/19594, WO 93/19749, WO 93/19750, WO 93/19751, WO 99/16766, WO 01/13953, WO 03/104204, WO 03/104205, WO 04/000814, WO 04/000839 and WO 04/005258 (Merck), WO 04018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/018431, WO 04/018449, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/019944, WO 04/019945, WO 04/045607, WO 04/037805, WO 04/063197, WO 04/103998, WO 04/111044, WO 05012252, WO 05012253, WO 05/013995, WO 05/030212, WO 05/030725, WO 05/087744, WO 05/087745, WO 05/087749 and WO 05/090345 as well as those described in WO 98/18796 and WO 03/39544; A2a agonists such as those described in EP 409595A2, EP 1052264, EP 1241176, WO 94/17090, WO 96/02543,

WO 96/02553, WO 98/28319, WO 99/24449, WO 99/24450, WO 99/24451, WO 99/38877, WO 99/41267, WO 99/67263, WO 99/67264, WO 99/67265, WO 99/67266, WO 00/23457, WO 00/77018, WO 00/78774, WO 01/23399, WO 01/27130, WO 01/27131, WO 01/60835, WO 01/94368, WO 02/00676, WO 02/22630, WO 02/96462, WO 03/086408, WO 04/039762, WO 04/039766, WO 04/045618 and WO 04/046083; and A2b antagonists such as those described in WO 02/42298 and WO 03/042214.

[000316] The bronchodilatory 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, beta-2 adrenoceptor agonists, anticholinergic agents, antimuscarinic agents, ipratropium bromide, oxitropium bromide, tiotropium salts, glycopyrrolate, CHF 4226 (Chiesi), SVT-40776, albuterol (salbutamol), metaproterenol, terbutaline, salmeterol, fenoterol, procaterol, formoterol, carmoterol, and GSK159797 and pharmaceutically acceptable salts thereof.

[000317] Other bronchodilatory 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, compounds (in free or salt or solvate form) of formula I of WO 0075114, preferably compounds of the Examples thereof, compounds (in free or salt or solvate form) of formula I of WO 04/16601 or of formula I of WO 04/087142, compounds, such as those described in EP 147719, EP 1440966, EP 1460064, EP 1477167, EP 1574501, JP 05025045, JP 2005187357, US 2002/0055651, US 2004/0242622, US 2004/0229904, US 2005/0133417, US 2005/5159448, US 2005/5159448, US 2005/171147, US 2005/182091, US 2005/182092, US 2005/209227, US 2005/256115, US 2005/277632, US 2005/272769, US 2005/239778, US 2005/215542, US 2005/215590, US 2006/19991, US 2006/58530, WO 93/18007, WO 99/64035, WO 01/42193, WO 01/83462, WO 02/66422, WO 02/ 70490, WO 02/76933, WO 03/24439, WO 03/42160, WO 03/42164, WO 03/72539, WO 03/91204, WO 03/99764, WO 04/16578, WO 04/22547, WO 04/32921, WO 04/33412, WO 04/37768, WO 04/37773, WO 04/37807, WO 04/39762, WO 04/39766, WO 04/45618 WO 04/46083 , WO 04/80964, WO 04/087142, WO 04/89892, WO 04/108675, WO 04/108676, WO 05/33121, WO 05/40103, WO 05/44787, WO 05/58867, WO 05/65650, WO 05/66140, WO 05/70908, WO 05/74924, WO 05/77361, WO 05/90288, WO 05/92860, WO 05/92887, WO 05/90287, WO 05/95328, WO 05/102350, WO 06/56471, WO 06/74897, WO 06/8173, EP 424021, US 3714357, US 5171744, US 2005/171147, US 2005/182091, WO 01/04118, WO 02/00652, WO 02/51841, WO 02/53564, WO 03/00840, WO 03/33495, WO 03/53966, WO 03/87094, WO 04/18422, WO 04/05285, WO 04/96800, WO 05/77361 and WO 06/48225.

[000318] Dual anti-inflammatory and bronchodilatory 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, dual beta-2 adrenoceptor agonist /muscarinic antagonists such as those disclosed in US 2004/0167167, US 2004/0242622, US 2005/182092, US 2005/256114, US 2006/35933, WO 04/74246, WO 04/74812, WO 04/89892 and WO 06/23475.

[000319] The antihistamine drug substances 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, cetirizine hydrochloride, levocetirizine, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride, activastine, astemizole, azelastine, dimetinden, ebastine, epinastine, levocabastine, mizolastine and tefenadine as well as those disclosed in WO 03/099807, WO 04/026841 and JP 2004107299.

[000320] 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, antimalarials, methothrexate, leflunomide, corticosteroids, cyclophosphamide, cyclosporin A, cyclosporin G, mycophenolate mofetil, ascomycin, rapamycin (sirolimus), FK-506, mizoribine, 15-deoxyspergualin, brequinar, mycophenolic acid, malononitriloamindes (such as, by way of example only, leflunamide), CTLA41g, 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 monoclonal antibodies include, but are not limited to, monoclonal antibodies for leukocyte receptors such as, by way of example only MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD45, CD58 or their ligands. 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, toll-like receptor (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).

[000321] In certain embodiments, the additional thereapeutic agent(s) used in the combination therapies described herein include, but are not limited to, agents such as tumour 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, Remicade, and Humira)); 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.

[000322] Chemotherapeutic agents or other anti-proliferative agents used in combination with the compounds provided herein to treat proliferative diseases and cancer include, but are not limited to, surgery, radiotherapy (γ-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes), endocrine therapy, biologic response modifiers (interferons, interleukins, and tumor necrosis factor (TNF)), hyperthermia and cryotherapy, agents to attenuate any adverse effects (e.g., antiemetics), and other chemotherapeutic drugs, including, but not limited to, anthracyclines, alkyl sulfonates, aziridines, ethylenimines, methylmelamines, nitrogen mustards, nitrosoureas, folic acid analogs, dihydrofolate reductase inhibitor, purine analogs, pyrimidine analogs, podophyllotoxins, platinum-containing agents, interferons, interleukins, alkylating agents (mechlorethamine, chlorambucil, Cyclophosphamide, Melphalan, Ifosfamide), antimetabolites (Methotrexate, gemcitabine or capecitabine), purine antagonists and pyrimidine antagonists (6-Mercaptopurine, 5-Fluorouracil, Cytarabile, Gemcitabine), spindle poisons/ microtubule active agents (Vinblastine, Vincristine, Vinorelbine, Paclitaxel, epothilone), topoisomerase I inhibitors, topoisomerase II inhibitors, podophyllotoxins (Etoposide, Irinotecan, Topotecan), antibiotics (Doxorubicin, Bleomycin, Mitomycin), nitrosoureas (Carmustine, Lomustine), inorganic ions (Cisplatin, Carboplatin), enzymes (Asparaginase), and hormones (Tamoxifen, Leuprolide, Flutamide, and Megestrol), GLEEVEC™, adriamycin, dexamethasone, cyclophosphamide, busulfan, improsulfan, piposulfan, benzodepa, carboquone, meturedepa, uredepa, altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, trimethylolomelamine, chlorambucil, chlornaphazine, cyclophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan,

novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, aclacinomycins, actinomycin F(1), anthramycin, azaserine, bleomycin, cactinomycin, carubicin, carzinophilin, chromomycin, dactinomycin, daunorubicin, daunomycin, 6-diazo-5-oxo-1-norleucine, doxorubicin, epirubicin, mitomycin C, mycophenolic acid, nogalamycin, olivomycin, peplomycin, plicamycin, porfiromycin, puromycin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, denopterin, methotrexate, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, fluorouracil, tegafur, L-asparaginase, pulmozyme, aceglatone, aldophosphamide glycoside, aminolevulinic acid, amsacrine, bestrabucil, bisantrene, carboplatin, cisplatin, defofamide, demecolcine, diaziquone, elfornithine, elliptinium acetate, etoglucid, etoposide, flutamide, gallium nitrate, hydroxyurea, interferon-alpha, interferon-beta, interferon-gamma, interleukin-2, lentinan, lonidamine, methotrexate, mitoguazone, mitoxantrone, mopidamol, nitracrine, pentostatin, phenamet, pirarubicin, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, sizofiran, spirogermanium, paclitaxel, tamoxifen, teniposide, tenuazonic acid, triaziquone or combinations thereof.

[000323] Other agents used in combination with the compounds provided herein include, but are not limited to: treatments for Alzheimer's Disease such as ARRICEPT™ and EXCELON™; treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., AVONEX™ and REBIF™), COPAXONE™, and mitoxantrone; treatments for asthma such as albuterol and SINGULAIR™; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophosphamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; and agents for treating immunodeficiency disorders such as gamma globulin.

[000324] In other embodiments the compounds of Formula (I) provided herein areused adjunct or adjuvant to other therapy, e.g. a therapy using a bone resorption inhibitor, for example as in osteoporosis therapy, in particular a therapy employing calcium, a calcitonin or an analogue or derivative thereof, e.g. salmon, eel or human calcitonin, a steroid hormone, e.g. an estrogen, a partial estrogen agonist or estrogen-

gestagen combination, a SERM (Selective Estrogen Receptor Modulator) e.g. raloxifene, lasofoxifene, TSE-424, FC1271, Tibolone (Livial A), vitamin D or an analog thereof or PTH, a PTH fragment or a PTH derivative e.g. PTH (1-84), PTH (1-34), PTH (1-36), PTH (1-38), PTH (1-31)NH2 or PTS 893.

Treatment of Diseases Mediated by Kinase Activity

[000325] Compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and combination therapies provided herein are modulators of Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and ALK kinase activity, and are used in the treatment and/or prevention of diseases and/or disorders in which aberrant, abnormal or deregulated activity of Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK contributes to the pathology and/or symptomology of such diseases and/or disorders. Such diseases and/or disorders mediated by Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK kinases are provided herein.

[000326] In certain embodiments, compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and combination therapies provided herein are inhibitors of Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and ALK kinase activity, and are used in the treatment and/or prevention of diseases and/or disorders in which aberrant, abnormal or deregulated activity of Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK contributes to the pathology and/or symptomology of such diseases and/or disorders. Such diseases and/or disorders mediated by Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK kinases are provided herein.

[000327] In certain embodiments, such diseases and/or disorders associated with aberrant, abnormal or deregulated activity of Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK kinases include, but are not limited to, cancer, proliferative diseases, pain, dermatological diseases and/or disorders, metabolic diseases and/or disorders, muscle diseases and/or disorders, neurodegenerative diseases and/or disorders, neurological diseases and/or disorders, immunodeficiency diseases and/or disorders, immunologically-mediated diseases and/or disorders, autoimmune diseases, autoimmune mediated diseases, bone diseases and/or disorders, inflammatory diseases, fibrosis, ophthalmic/occular diseases and/or disorders, infectious diseases, viral diseases, wound repair, respiratory diseases and/or disorders, pulmonary diseases and/or disorders, renal disease, kidney disease, liver disease, cardiovascular diseases and/or disorders, vascular diseases and/or disorders heart disease, cell death and hyperplasia.

[000328] Such cancer and proliferative diseases include, but are not limited to, hematopoietic disorders, hematopoietic malignancies, non-hematopoietic malignancies, benign or malignant tumors, tumors of the

neck and head, brain cancer, kidney cancer, liver cancer, adrenal gland cancer, neuronal cancer, neuroblastoma, bladder cancer, breast cancer, secretory breast carcinoma, stomach cancer, gastric tumors, ovarian cancer, uterine cancer, colon cancer, rectal cancer, colorectal adenoma, prostate cancer, renal cancer, brain cancer, endometrial cancer, pancreatic cancer, lung cancer, non-small cell lung cancer, human adenoid cystic carcinoma, vaginal cancer, thyroid cancer, papillary thyroid carcinoma, sarcoma, congenital fibrosarcoma, osteolytic sarcoma, osteosarcoma, fibrosarcoma, myeloma, tumor metastasis to bone, congenital mesoblastic nephroma, glioblastomas, melanoma, multiple myeloma, gastrointestinal cancer, gastrointestinal stromal tumors (GIST), mastocytosis, neuroblastoma, fibrotic cancers, tumor metastasis growth, epidermal hyperproliferation, psoriasis, metastasis, prostate hyperplasia, neoplasia, neoplasia of epithelial character, lymphomas, diffuse large B-cell lymphoma, B-cell lymphoma, mammary carcinoma, Wilm's tumor, Cowden syndrome, Lhermitte-Dudos disease and Bannayan-Zonana syndrome.

[000329] Such hematopoietic disorders include, but are not limited to, myeloproliferative disorders, thrombocythemia, essential thrombocytosis (ET), angiogenic myeloid metaplasia, myelofibrosis (MF), myelofibrosis with myeloid metaplasia (MMM), chronic idiopathic myelofibrosis (IMF), polycythemia vera (PV), the cytopenias, and pre-malignant myelodysplastic syndromes.

[000330] Such hematological malignancies include, but are not limited to, leukemias, myeloid leukemias, hairy cell leukemia, lymphomas (non-Hodgkin's lymphoma), Hodgkin's disease (also called Hodgkin's lymphoma), and myeloma, including, but are not limited to, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL), anaplastic large-cell lymphoma (ALCL), prolymphocytic leukemia (PML), juvenile myelomonocyctic leukemia (JMML), adult T-cell ALL, AML with trilineage myelodysplasia (AML/TMDS), mixed lineage leukemia (MLL), myelodysplastic syndromes (MDSs), myeloproliferative disorders (MPD), multiple myeloma, (MM), myeloid sarcoma and acute promyelocytic leukemia (APL).

[000331] Such pain disorders include, but are not limited to, cancer-related pain, skeletal pain caused by tumor metastasis, osteoarthritis, visceral pain, inflammatory pain and neurogenic pain.

[000332] Such dermatological diseases and/or disorders include, but are not limited to, inflammatory or allergic conditions of the skin, dermatitis, eczema, psoriasis, atopic dermatitis, seborrhoeic dermatitis (Dandruff, Cradle cap), diaper rash, urushiol-induced contact dermatitis, contact dermatitis, erythroderma, lichen simplex chronicus, prurigo nodularis, itch, pruritus ani, nummular dermatitis, dyshidrosis, pityriasis alba, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphigus, epidermolysis bullosa acquisita, peritoneal and sub dermal adhesion and photoaging of the skin.

[000333] Such metabolic diseases and/or disorders and eating disorder include, but are not limited to, obesity, diabetes and anoerexia.

[000334] Such muscle diseases and/or disorders include, but are not limited to, muscular atrophies (e.g. disuse), muscular dystrophies (e.g. Duchenne's muscle dystrophy, Becker's muscle dystrophy, Limb-Girdle muscle dystrophy), sarcopenia, cachexia, wasting and Facioscapulohumeral dystrophy.

[000335] Such neurological diseases and/or disorders and neurodegenerative disorders include, but are not limited to, impaired neurological function and Alzheimer's disease.

[000336] Such immunodeficiency diseases and/or disorders and immunologically-mediated diseases and/or disorders include, but are not limited to, pathologic immune conditions involving T cell activation, anaphylaxis, allergy and psoriasis. Such allergy disorders include, but are not limited to, respiratory diseases and dermatolgical disorders.

[000337] Such immunological- mediated disorders include, but are not limited to, allergy and psoriasis. Such allergy disorders include, but are not limited to, respiratory diseases and dermatolgical disorders.

[000338] Such autoimmune diseases and/or disorders and autoimmune-mediated diseases and/or disorders include, but are not limited to, destructive arthritis, rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, multiple sclerosis, dermatomyositis, progressive systemic sclerosis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or aetiology, including autoimmune haematological disorders (e.g. haemolytic anaemia, aplastic anaemia, pure red cell anaemia, idiopathic thrombocytopenic purpura and idiopathic thrombocytopenia), primary binary cirrhosis (PBC), lupus, systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary billiary cirrhosis, uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

[000339] Such bone diseases and/or disorders include, but are not limited to, osteoporosis, osteitis deformans, Paget's disease, osteoarthritis, prosthesis failure, osteopenia, and fractures and other disorders in which low bone mineral density are a hallmark of the disease.

[000340] Such inflammatory diseases and/or disorders include, but are not limited to, uveitis, atherosclerosis, atherogenesis, glomerulonephritis, Kawasaki disease, inflammatory responses, polymyositis, arthritis, neurological inflammation, chronic arthritis inflammation and osteoarthritis.

[000341] Such fibrosis diseases and/or disorders include, but are not limited to, extracellular matrix accumulation and fibrosis, scleroderma, fibrosclerosis, radiation-induced fibrosis, kidney fibrosis, lung fibrosis and liver fibrosis, haemochromatosis, primary biliary cirrhosis, restenosis, retroperitoneal fibrosis, mesenteric fibrosis, endometriosis and keloids.

[000342] Such ophthalmic/ocular diseases and/or disorders include, but are not limited to, proliferative vitreoretinopathy, ocular scarring, corneal scarring, ocular disorders, corneal wounds, conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis.

[000343] Such infectious and viral diseases and/or disorders include, but are not limited to, HIV-1 infection, for example, hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-induced hepatitis.

[000344] Wound repair includes, but are not limited to, excessive or hypertrophic scar or keloid formation in the dermis occurring during wound healing resulting from trauma or surgical wounds, ulcers (including diabetic ulcers, chronic ulcers, gastric ulcers, and duodenal ulcers).

[000345] Such respiratory diseases and/or disorders and pulmonary disorders include, but are not limited to, asthma, bronchial asthma, allergic asthma, intrinsic (non-allergic) asthma, extrinsic (allergic) asthma, exercise-induced asthma, drug-induced asthma (including aspirin and NSAID-induced) and dust-induced asthma, chronic obstructive pulmonary disease (COPD); chronic obstructive airways disease (COAD), chronic obstructive lung disease (COLD), bronchitis, chronic bronchitis, acute bronchitis, dyspnea, arachidic bronchitis, catarrhal bronchitis, croupus bronchitis, phthinoid bronchitis, rhinitis, acute rhinitis, chronic rhinitis, rhinitis medicamentosa, vasomotor rhinitis, perennial and seasonal allergic rhinitis, rhinitis nervosa (hay fever), inflammatory or obstructive airways diseases, pulmonary hypertension, acute lung injury, adult/acute respiratory distress syndrome (ARDS), pulmonary fibrosis, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, pulmonary disease due to infectious or toxic agents, emphysema, pneumoconiosis, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis, byssinosis, acute lung injury (ALI), hypereosinophilia, Löffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma, eosinophil-related disorders affecting the airways occasioned by drug-reaction, pulmonary hypertension, primary pulmonary hypertension (PPH), secondary pulmonary hypertension (SPH), familial PPH, sporadic PPH, precapillary pulmonary hypertension, pulmonary arterial hypertension (PAH), pulmonary artery hypertension, idiopathic pulmonary hypertension, thrombotic pulmonary arteriopathy (TPA), plexogenic pulmonary arteriopathy, functional classes I to IV pulmonary hypertension, and pulmonary hypertension associated with, related to, or secondary to, left ventricular dysfunction, mitral valvular disease, constrictive pericarditis, aortic stenosis, cardiomyopathy, mediastinal fibrosis, anomalous pulmonary venous drainage, pulmonary venoocclusive disease, collagen vascular disease, congenital heart disease, HIV virus infection, drugs and toxins such as fenfluramines, hypoxemia, pulmonary venous hypertension, chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorder, chronic exposure to high altitude, neonatal lung disease, alveolar-capillary dysplasia, sickle cell disease, other coagulation disorder, chronic thromboemboli, connective tissue disease, lupus, schistosomiasis, sarcoidosis or pulmonary capillary hemangiomatosis.

[000346] Such renal diseases and/or disorders include, but are not limited to, glomerulonephritis, renal interstitial fibrosis, renal fibrosis, chronic renal disease and acute renal disease. Such kidneey diseases and/or disorders include, but are not limited to, diabetic nephropathy, lupus nephritis, hypertension-induced nephropathy, HIV-associated nephropathy and transplant necropathy. Such liver diseases and/or disorders include, but are not limited to, hepatic dysfunction attributable to infections, alcohol- induced hepatitis, disorders of the biliary tree and hepatic ischemia.

[000347] Such cardiovascular, vascular or heart diseases and/or disorders include, but are not limited to, congestive heart failure, post-infarction cardiac fibrosis, congestive heart failure, reperfusion/ischemia in stroke, heart attacks, and organ hypoxia, ischemia, dilated cardiomyopathy, myocarditis, myocardial infarction vascular stenosis, restenosis, atherosclerosis, male erectile dysfunction, Raynaud's syndrome, thrombosis and thrombin-induced platelet aggregation.

[000348] In other embodiments the compounds of Formula (I) provided herein are immunosuppressive agents and are used to treat organ transplant rejection, chronic transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, dermatitis, Crohn's disease, type-1 diabetes and complications from type-1 diabetes.

[000349] 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 and/or prevention 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, acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever).

[000350] 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 and/or prevention of dermatological disorders including, but not limited to, psoriasis, dermatitis, eczema, atopic dermatitis, contact dermatitis, urushiol-induced contact dermatitis, eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen simplex chronicus, lichen planus, lichen sclerosus et atrophica, discoid lupus erythematosus, diaper rash, erythroderma, prurigo nodularis, itch, pruritus ani, nummular dermatitis, dyshidrosis and pityriasis alba.

[000351] 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 and/or prevention of cancer including, but not limited to, hematopoietic disorders, hematopoietic malignancies, non-hematopoietic malignancies, benign or

malignant tumors, tumors of the neck and head, brain cancer, kidney cancer, liver cancer, adrenal gland cancer, neuronal cancer, neuroblastoma, bladder cancer, breast cancer, secretory breast carcinoma, stomach cancer, gastric tumors, ovarian cancer, uterine cancer, colon cancer, rectal cancer, colorectal adenoma, prostate cancer, renal cancer, brain cancer, endometrial cancer, pancreatic cancer, lung cancer, non-small cell lung cancer, human adenoid cystic carcinoma, vaginal cancer, thyroid cancer, papillary thyroid carcinoma, sarcoma, congenital fibrosarcoma, osteolytic sarcoma, osteosarcoma, fibrosarcoma, myeloma, tumor metastasis to bone, congenital mesoblastic nephroma, glioblastomas, melanoma, multiple myeloma, gastrointestinal cancer, gastrointestinal stromal tumors (GIST), mastocytosis, neuroblastoma, fibrotic cancers, tumor metastasis growth, epidermal hyperproliferation, psoriasis, metastasis, prostate hyperplasia, neoplasia, neoplasia of epithelial character, lymphomas, diffuse large B-cell lymphoma, B-cell lymphoma, mammary carcinoma, Wilm's tumor, Cowden syndrome, Lhermitte-Dudos disease and Bannayan-Zonana syndrome.

[000352] 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 and/or prevention of cancer including, but not limited to, hematopoietic disorders, hematopoietic malignancies, non-hematopoietic malignancies, benign or malignant tumors, tumors of the neck and head, brain cancer, kidney cancer, liver cancer, adrenal gland cancer, neuronal cancer, neuroblastoma, bladder cancer, breast cancer, secretory breast carcinoma, stomach cancer, gastric tumors, ovarian cancer, uterine cancer, colon cancer, rectal cancer, colorectal adenoma, prostate cancer, renal cancer, brain cancer, endometrial cancer, pancreatic cancer, lung cancer, non-small cell lung cancer, human adenoid cystic carcinoma, vaginal cancer, thyroid cancer, papillary thyroid carcinoma, sarcoma, congenital fibrosarcoma, osteolytic sarcoma, osteosarcoma, fibrosarcoma, myeloma, tumor metastasis to bone, congenital mesoblastic nephroma, glioblastomas, melanoma, multiple myeloma, gastrointestinal cancer, gastrointestinal stromal tumors (GIST), mastocytosis, neuroblastoma, fibrotic cancers, tumor metastasis growth, epidermal hyperproliferation, psoriasis, metastasis, prostate hyperplasia, neoplasia, neoplasia of epithelial character, lymphomas, diffuse large B-cell lymphoma, B-cell lymphoma, mammary carcinoma, Wilm's tumor, Cowden syndrome, Lhermitte-Dudos disease and Bannayan-Zonana syndrome. Such hematopoietic disorders include, but are not limited to, myeloproliferative disorders, thrombocythemia, essential thrombocytosis (ET), angiogenic myeloid metaplasia, myelofibrosis (MF), myelofibrosis with myeloid metaplasia (MMM), chronic idiopathic myelofibrosis (IMF), polycythemia vera (PV), the cytopenias, and pre-malignant myelodysplastic syndromes. Such hematological malignancies include, but are not limited to, leukemias, myeloid leukemias, hairy cell leukemia, lymphomas (non-Hodgkin's lymphoma), Hodgkin's disease (also called Hodgkin's lymphoma), and myeloma, including, but are not limited to, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML),

chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL), anaplastic large-cell lymphoma (ALCL), prolymphocytic leukemia (PML), juvenile myelomonocyctic leukemia (JMML), adult T-cell ALL, AML with trilineage myelodysplasia (AML/TMDS), mixed lineage leukemia (MLL), myelodysplastic syndromes (MDSs), myeloproliferative disorders (MPD), multiple myeloma, (MM), myeloid sarcoma and acute promyelocytic leukemia (APL).

[000353] In certain embodiments, the compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, and pharmaceutical compositions and combination therapies provided herein are used as immunosuppressant agents to treat and/or prevent rheumatoid arthritis (RA), multiple sclerosis (MS), systemic lupus erythematosus (SLE), immune thrombocytopenic purpura (ITP), hemolytic anemia and transplant rejection.

[000354] Compounds of Formula (I), pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, pharmaceutical compositions, and combination therapies provided herein are used in methods for modulating Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and ALK kinase activity in a subject (human or other mammal) for the treatment and/or prevention of diseases and/or disorders associated with or mediated by aberrant, abnormal or deregulated Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK kinase activity. In certain embodiments, such methods include administering to a subject an effective amount of a compound of Formula (I), or a pharmaceutical composition containing a compound of Formula (I).

[000355] In certain embodiments, the methods for the treatment of a subject suffering from a disease and/or disorder associated with aberrant, abnormal or deregulated Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK kinase activity include administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate thereof, either alone or as part of a pharmaceutical composition as described herein.

[000356] 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 aberrant, abnormal or deregulated Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK kinase activity. In other embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is used in the treatment of a disease or disorder associated with aberrant, abnormal or deregulated Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK kinase activity.

[000357] In a further embodiment, pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for oral administration for the treatment of a disease or disorder associated with

aberrant, abnormal or deregulated Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK kinase activity. In a further embodiment, pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for topical administration for the treatment of a disease or disorder associated with aberrant, abnormal or deregulated Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK kinase activity. In a further embodiment, pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for parenteral administration for the treatment of a disease or disorder associated with aberrant, abnormal or deregulated Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK kinase activity. In a further embodiment, pharmaceutical compositions comprising at least one compound of Formula (I) are adapted for pulmonary/inhalation administration for the treatment of a disease or disorder associated with aberrant, abnormal or deregulated Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK kinase activity.

[000358] In certain embodiments, the system or subject used in the methods provided herein are cell or tissue systems. In certain embodiments, the system or subject used in the methods provided herein are human or animal subjects.

[000359] In accordance with the foregoing, provided herein are methods for preventing, treating and/or ameliorating the condition of any of the diseases or disorders described above in a subject in need of such treatment, which method comprises administering to said subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. For any of the methods and uses provided herein, the required dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired.

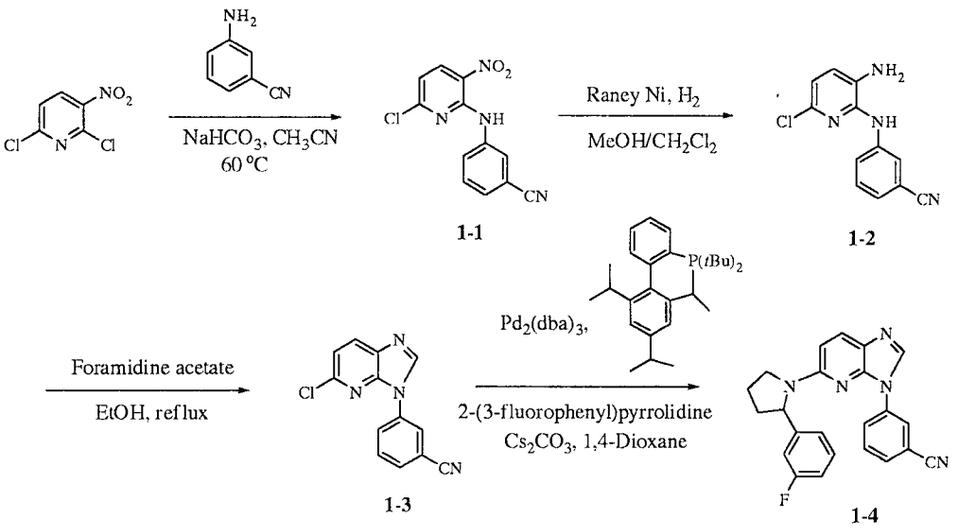
Kits

[000360] Also provided herein are pharmaceutical packs or kits that include one or more containers containing a compound of Formula (I) useful for the treatment or prevention of a disease or disorder mediated by Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK kinases. In other embodiments, such pharmaceutical packs or kits include one or more containers containing a compound of Formula (I) useful for the treatment or prevention of a disease or disorder mediated by Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK kinases 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).

Examples

[000361] The following examples are offered to illustrate, but not to limit, the compounds of Formula (I) provided herein, and the preparation of such compounds.

Scheme 1



Example 1

Preparation of 3-(5-(2-(3-Fluorophenyl)pyrrolidin-1-yl)-3H-imidazo [4,5-b]pyridin-3-yl)benzonitrile

[000362] 3-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile (1-4) was synthesized in four steps as shown in scheme 1.

[000363] In step 1-1, sodium bicarbonate (1.68g, 20 mmol) was added into a solution of 2,6-dichloro-3-nitropyridine (1.93g, 10 mmol) and 3-amino benzonitrile (1.18g, 10 mmol) in acetonitrile and the suspension was heated for 24 hours at 60 °C. The mixture was filtered and washed twice with water to give 3-(6-chloro-3-nitropyridin-2-ylamino)benzonitrile (1-1) as a pale yellow solid. ^{1}H NMR DMSO-d6 δ (ppm) 10.24 (s, 1H), 8.57 (d, 1H), 8.09 (m, 1H), 7.93 (m, 1H), 7.62 (m, 2H), 7.08 (d, 1H); *m/z* 357 M+1.

[000364] In step 1-2, Raney nickel was added to a suspension of 3-(6-chloro-3-nitropyridin-2-ylamino)benzonitrile in methanol/ dichloromethane (1: 1) and the resulting suspension was set up in Parr shaker under a hydrogen atmosphere (40 psi) for 18 hours. The remaining catalyst was removed through a Celite pad, and the reaction mixture was concentrated to afford the crude product 3-(3-amino-6-chloropyridin-2-ylamino)benzonitrile (1-2) which was used in the next step without further purification.

[000365] In step 1-3, a solution of 3-(3-amino-6-chloropyridin-2-ylamino)benzonitrile (1.07g, 4.38 mmol) and foramidine acetate (1.37g, 13.1 mmol) in ethanol was refluxed for 3 hours. The reaction mixture was concentrated and purified to afford 3-(5-chloro-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile (1-

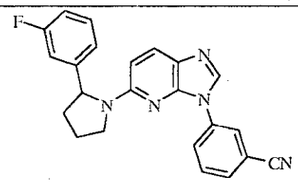
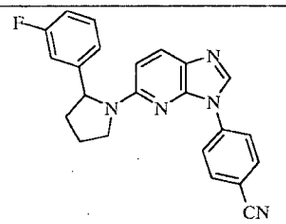
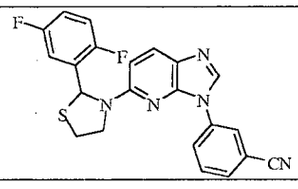
59

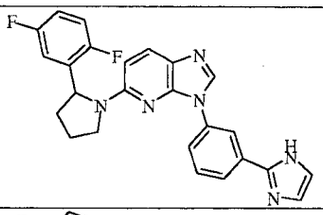
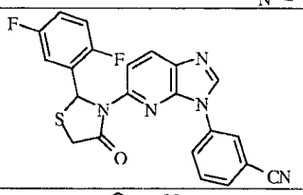
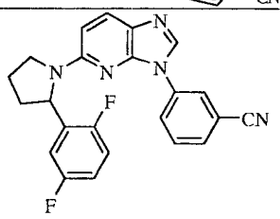
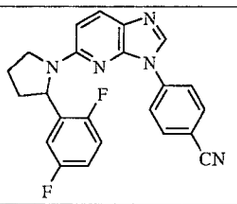
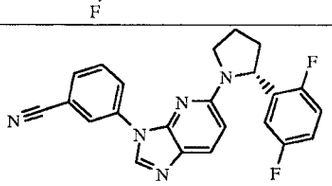
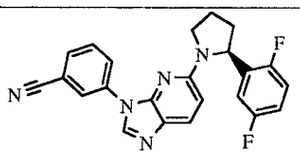
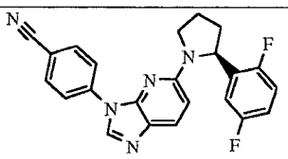
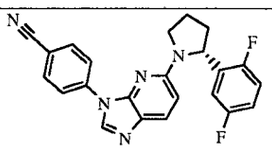
3) as a yellow solid.

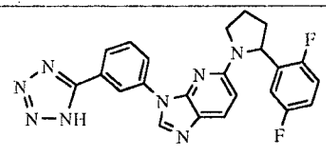
[000366] In step 1-4, *tris*(dibenzylideneacetone) dipalladium (0) (10.8mg, 0.012 mmol), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (22mg, 0.047 mmol) and cesium carbonate (77mg, 0.24 mmol) were added consecutively into a solution of 3-(5-chloro-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile (30mg, 0.12 mmol) and 2-(3-fluorophenyl)pyrrolidine (29mg, 0.18 mmol) in 1,4-dioxane. The mixture was degased under house vacuum, and charged with nitrogen and heated for 18 hours at 100 °C. The reaction mixtures was purified using HPLC to afford 3-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile (1-4) as a white solid. ^{1}H NMR methanol-d4 δ (ppm) 8.86 (s, 1H), 8.28 (s, 1H), 7.98 (m, 1H), 7.89 (d, 1H), 7.78 (d, 1H), 7.63 (t, 1H), 7.33 (m, 1H), 7.09 (dm, 1H), 6.93(m, 2H), 6.70 (d, 1H), 5.18 (d, 1H), 3.94 (m, 1H), 3.68 (m, 1H), 2.48 (m, 1H), 2.11 (m, 2), 1.97 (m, 1H); *m/z* 384 (M+1).

[000367] By repeating the procedures described in the above examples, using appropriate starting materials, the following compounds of Formula I, as identified in Table 1, were obtained.

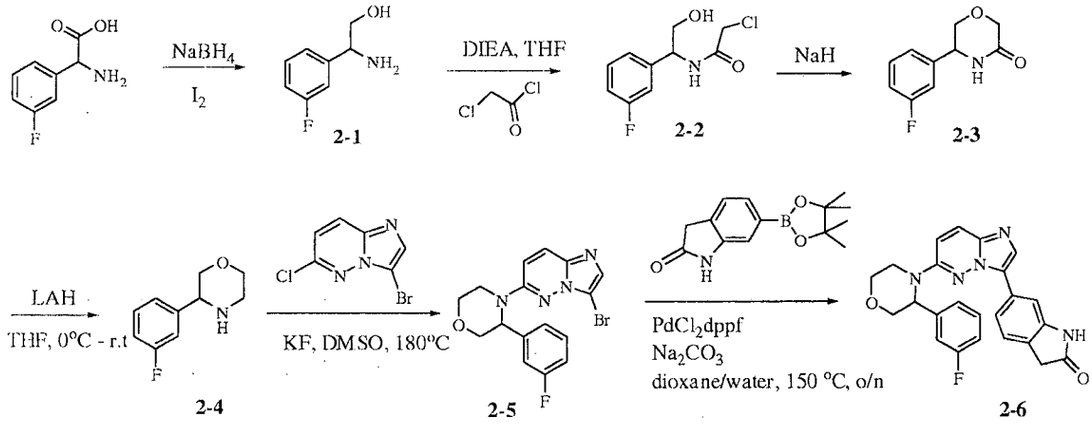
Table 1

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
1		^{1}H NMR methanol-d4 δ (ppm) 8.86 (s, 1H), 8.28 (s, 1H), 7.98 (m, 1H), 7.89 (d, 1H), 7.78 (d, 1H), 7.63 (t, 1H), 7.33 (m, 1H), 7.09 (dm, 1H), 6.93(m, 2H), 6.70 (d, 1H), 5.18 (d, 1H), 3.94 (m, 1H), 3.68 (m, 1H), 2.48 (m, 1H), 2.11 (m, 2), 1.97 (m, 1H); *m/z* 384 (M+1)
2		^{1}H NMR methanol-d4 δ (ppm) 8.79 (s, 1H), 7.89 (m, 3H), 7.80 (m, 2H), 7.36 (m, 1H), 7.09 (d, 1H), 6.99 (m, 2H), 6.70 (d, 1H), 5.13 (dd, 1H), 3.94 (m, 1H), 3.69 (m, 1H), 2.49 (m, 1H), 2.11 (m, 2H), 1.97 (m, 1H); *m/z* 384 (M+1)
3		*m/z* 420 (M+1)

4		*m/z* 443 (M+1)
5		*m/z* 443 (M+1)
6		MS *m/z* 402 (M+1)
7		MS *m/z* 402 (M+1)
8		MS *m/z* 402 (M+1)
9		MS *m/z* 402 (M+1)
10		MS *m/z* 402 (M+1)
11		MS *m/z* 402 (M+1)

12		MS *m/z* 402 (M+1)

Scheme 2



Example 2

6-(6-(3-(3-Fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)indolin-2-one

[000368] 6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)indolin-2-one (2-6) was synthesized in six steps as shown in scheme 2.

[000369] In step 2-1, D,L-3-fluorophenylglycine (10 g, 59.2 mmol) was added to a suspension of $NaBH_4$ (5.37 g, 142 mmol) in THF (200 mL). The suspension was cooled to 0 °C, and an iodine (15 g, 59.2 mmol) solution in THF was added drop-wise. The resulting solution was heated while stirring over-night. This solution was cooled to room temperature, quenched with a 20 % KOH solution (150 mL), and extracted with dichloromethane (3x). The organics were combined, dried over $MgSO_4$ and the solvent removed using a rotary evaporator. The product was purified with flash chromatography (0 -10 % methanol/ethyl acetate) to yield 2-amino-2-(3-fluorophenyl)ethanol (2-1) as a white residue.

[000370] In step 2-2, triethylamine (8.15 mL, 58.6 mmol) in a single portion was added to a solution of 2-amino-2-(3-fluorophenyl)ethanol (7.57 g, 48.8 mmol) in THF cooled to 0 °C and chloroacetyl chloride (5.08 mL, 58.6 mmol) was added drop-wise. The mixture was cooled to 0°C and stirred for 1 hour. The reaction mixture was quenched with water and the organic phase was washed with 0.5 N HCl, saturated $NaHCO_3$, brine, and dried over $MgSO_4$. The organic phase was concentrated and purified with flash chromatography (50 % EtOAc/hexanes) to yield 2-chloro-*N*-(1-(3-fluorophenyl)-2-hydroxyethyl)acetamide (2-2) as a yellow solid.

[000371] In step 2-3, a solution of 2-chloro-*N*-(1-(3-fluorophenyl)-2-hydroxyethyl)acetamide (5.5 g, 24

mmol) in THF (150 mL) was slowly added to a suspension of NaH (1.05 g, 26 mmol) in THF (600 mL) at 0 °C. The heterogeneous solution was warmed to room temperature and stirred overnight. The reaction mixtures was quenched, concentrated and ethyl acetate was added to the residue. This solution was washed with water and brine and the organic phase was dried over $MgSO_4$, filtered and concentrated to yield 5-(3-fluorophenyl)morpholin-3-one (2-3).

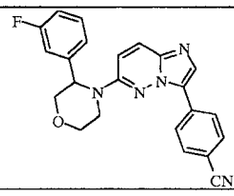
[000372] In step 2-4, a solution of 5-(3-fluorophenyl)morpholin-3-one (4.56 g, 23.4 mmol) in THF at 0 °C was treated with lithium aluminum hydride (4.3 g, 107 mmol) in a single portion. The suspension was warmed to room temperature and stirred overnight. The reaction mixture was quenched with $Na_2SO_4 \cdot 10$ H_2O and stirred for 4 hours. The heterogeneous solution was filtered through a celite pad, and the filtrate was concentrated and purified with flash chromatography (5-10 % methanol/EtOAc) to obtain 3-(3-fluorophenyl)morpholine (2-4) as a clear oil. ^{1}H NMR CDCl3 (δ) ppm 7.28 (m, 1H), 7.13 (m, 2H), 6.97 (m, 1H), 3.93 (dd, 1H), 3.89 (m, 1H), 3.81 (dd, 1H), 3.64 (td, 1H), 3.35 (m, 1H), 3.12 (td, 1H), 3.02 (m, 1H).

[000373] In step 2-5, a suspension of 3-(3-fluorophenyl)morpholine (1.59 g, 6.9 mmol), 3-bromo-6-chloroimidazo[1,2-b]pyridazine (12-1) (1.5 g, 8.29 mmol) and potassium fluoride (1.6 g, 27.6 mmol) in DMSO (6 mL) was heated at 180 °C for 18 hours while stirring. The resulting solution was cooled to room temperature and purified with HPLC to yield 4-(3-Bromoimidazo[1,2-b]pyridazin-6-yl)-3-(3-fluorophenyl)morpholine (2-5) as a yellow foam.

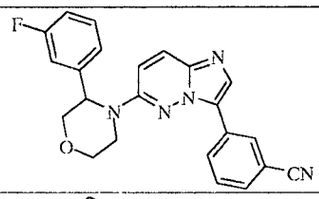
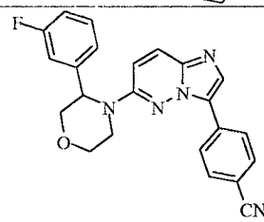
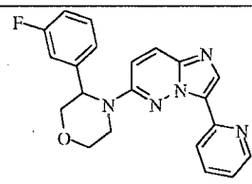
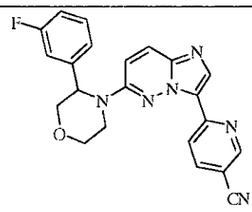
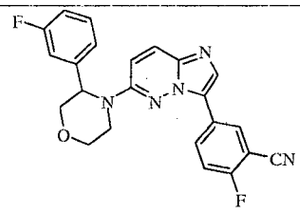
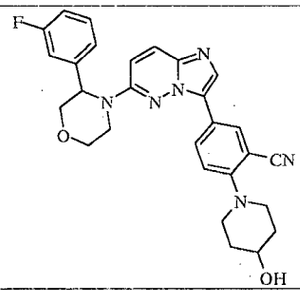
[000374] In step 2-6, a suspension of 4-(3-bromoimidazo[1,2-b]pyridazin-6-yl)-3-(3-fluorophenyl)morpholine (25 mg, 0.067 mmol), 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-2-one (34 mg, 0.13 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (2.7 mg, 0.0033 mmol) in 3 mL of 1, 4-dioxane and 0.5 mL of 2.0M sodium carbonate was bubbled with nitrogen and heated to 150 °C and stirred for 20 hours. The solution was cooled to room temperature and purified with HPLC to afford 6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)indolin-2-one (2-6) as a white solid.

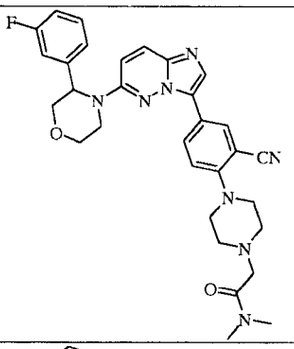
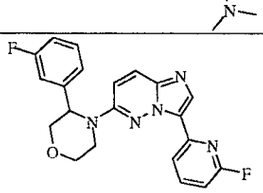
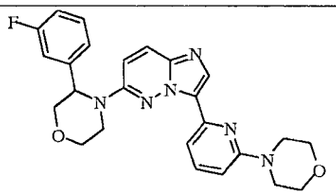
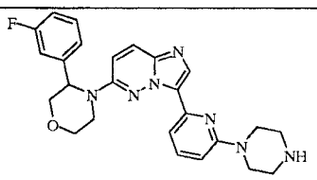
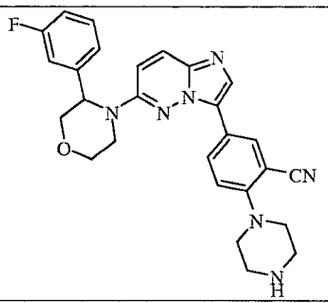
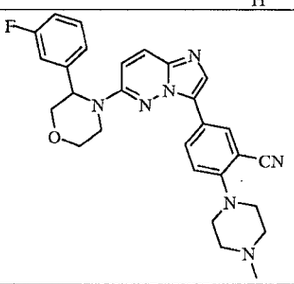
[000375] By repeating the procedures described in the above examples, using appropriate starting materials, the following compounds of Formula I, as identified in Table 2, were obtained.

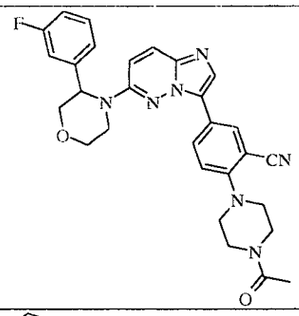
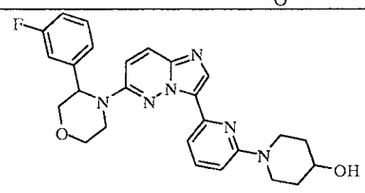
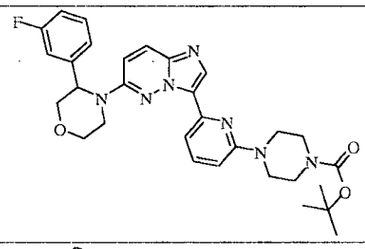
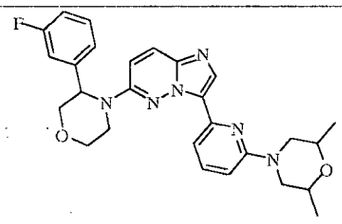
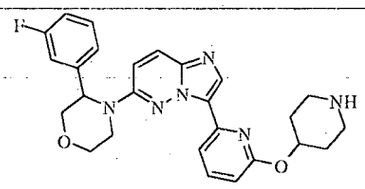
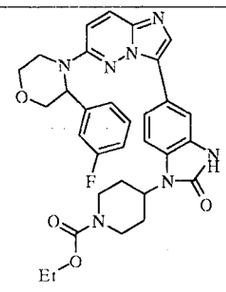
Table 2

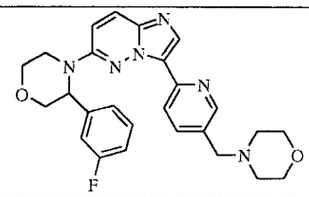
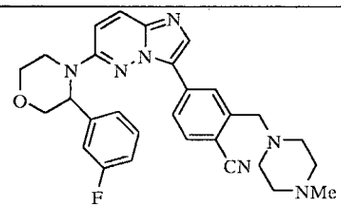
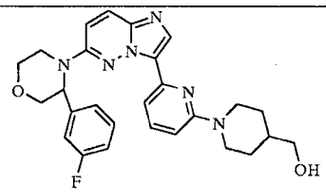
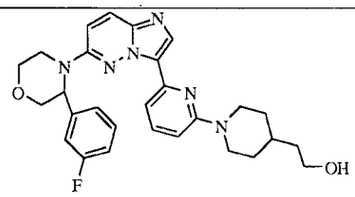
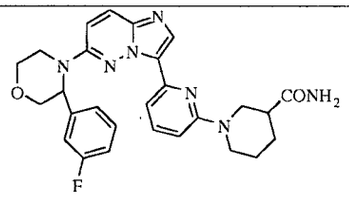
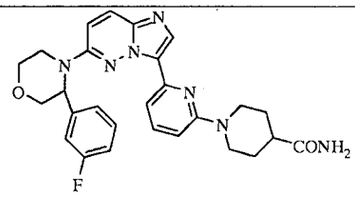
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
1		^{1}H NMR methanol-d4 δ (ppm) 7.97 (m, 3H), 7.72 (d, 2H), 7.66 (b, 1H), 7.45 (s, 1H), 2.24 (q, 1H), 7.11 (d, 1H), 7.07 (m, 1H), 6.89 (m, 1H), 5.17 (m, 1H), 1.46 (dd, 1H), 4.00 (m, 3H), 3.76 (m,

61

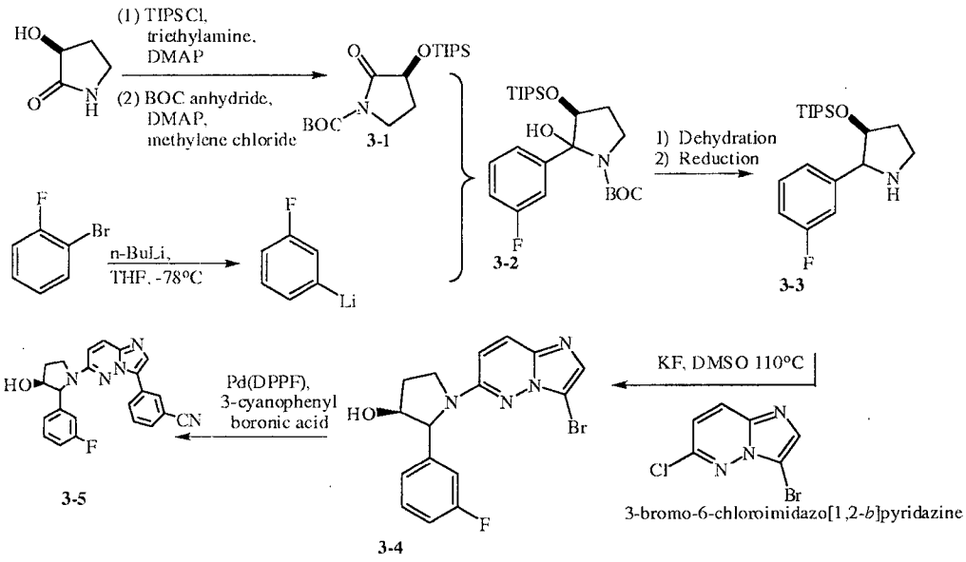
		1H), 3.66 (m, 1H); *m/z* 400 (M+1)
2		*m/z* 400 (M+1)
3		^{1}H NMR methanol-d4 δ (ppm) 7.97 (m, 3H), 7.72 (d, 2H), 7.66 (b, 1H), 7.45 (s, 1H), 2.24 (q, 1H), 7.11 (d, 1H), 7.07 (m, 1H), 6.89 (m, 1H), 5.17 (m, 1H), 1.46 (dd, 1H), 4.00 (m, 3H), 3.76 (m, 1H), 3.66 (m, 1H); *m/z* 400 (M+1)
4		^{1}H NMR $CDCl_3$ δ (ppm) 8.72 (s, 1H), 8.49 (d, 1H), 8.30 (s, 1H), 8.08 (d, 1H), 7.84 (t, 1H), 7.39 (m, 1H), 7.26 (m, 2H), 7.03 (m, 2H), 6.91 (m, 1H), 5.08 (s, 1H), 4.22 (dd, 1H), 4.06 (m, 2H), 3.92 (m, 1H), 3.81 (m, 1H), 3.67 (m, 1H); *m/z* 376 (M+1)
5		*m/z* 401 (M+1)
6		*m/z* 418 (M+1)
7		*m/z* 499 (M+1)

8		*m/z* 569 (M+1)
9		*m/z* 394 (M+1)
10		^{1}H NMR methanol-d4 δ (ppm) 8.43 (s, 1H), 8.12 (d, 1H), 7.69 (m, 3H), 7.34 (m, 1H), 7.25 (m, 2H), 7.00 (m, 1H), 6.88 (dd, 1H), 5.39 (m, 1H), 4.33 (dd, 1H), 4.15 (m, 3H), 3.82 (m, 6H), 3.58 (m, 4H); *m/z* 461 (M+1)
11		^{1}H NMR methanol-d4 δ (ppm) 8.50 (s, 1H), 8.14 (d, 1H), 7.77 (m, 3H), 7.36 (m, 1H), 7.36 (m, 2H), 7.01 (m, 2H), 5.40 (m, 1H), 4.34 (dd, 1H), 4.14 (m, 3H), 3.91 (m, 6H), 3.77 (m, 1H), 3.34 (m, 5H); *m/z* 460 (M+1)
12		*m/z* 484 (M+1)
13		^{1}H NMR methanol-d4 δ (ppm) 8.31 (d, 1H), 8.22 (s, 1H), 8.12 (m, 2H), 7.72 (d, 1H), 7.34 (m, 2H), 7.23 (d, 1H), 7.16 (m, 1H), 6.97 (m, 1H), 5.29 (m, 1H), 4.27 (dd, 1H), 4.05 (m, 3H), 3.86 (m, 3H), 3.72 (m, 3H), 3.45 (m, 4H), 3.03 (s, 3H); *m/z* 498 (M+1)

14		*m/z* 526 (M+1)
15		*m/z* 475 (M+1)
16		*m/z* 560 (M+1)
17		^{1}H NMR DMSO-d6 δ (ppm) 8.12 (m, 1H), 7.95 (m,1H), 7.59 (d, 1H), 7.51 (t, 1H), 7.20 (m, 4H), 6.97 (td, 1H), 6.71 (d, 1H), 5.23 (m, 1H), 4.16 (m, 3H), 3.97 (m, 3H), 3.71 (td, 1H), 3.56 (m, 3H), 2.33 (m, 2H), 1.12 (s, 3H), 1.10 (s, 3H); *m/z* 489 (M+1)
18		*m/z* 475 (M+1)
19		^{1}H NMR methanol-d4 δ (ppm) 8.18 (s, 1H), 8.12 (d, 1H), 7.73 (m, 2H), 7.56 (dd, 1H), 7.34 (d, 1H), 7.28 (m,1H), 7.20 (m, 2H), 6.96 (m, 1H), 5.29 (m, 1H), 4.51 (m, 1H), 4.36 (m, 3H), 4.18 (q, 2H), 4.09 (m, 3H), 3.87 (td, 1H), 3.74 (m, 1H), 3.00 (m, 2H), 2.41 (m, 2H), 1.85 (m, 2H), 1.31 (t, 3H); *m/z* 586 (M+1)

20		MS *m/z* 475 (M+1)
21		MS *m/z* 512 (M+1)
22		MS *m/z* 489 (M+1)
23		MS *m/z* 503 (M+1)
24		MS *m/z* 502 (M+1)
25		MS *m/z* 502 (M+1)

Scheme 3



Example 3

3-(6-((3S)-2-(3-fluorophenyl)-3-hydroxypyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile

[000376] 3-(6-((3S)-2-(3-fluorophenyl)-3-hydroxypyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile (3-5) was synthesized in five steps as shown in scheme 3.

[000377] In step 3-1, triethylamine (20 ml ,139 mmol), p-N,N-dimethylaminopyridine (150 mg, 1 mmol) and then triisopropylsilyl chloride (22.6 grams, 118 mmol) were added dropwise over 4 minutes to a solution of *S*-3-hydroxy-2-pyrrolidinone (4.00 grams, 39.6 mmol) in 40 mL of methylene chloride. The reaction mixture was stirred for 3 days and was then quenched with 200 mL of brine. The solution was extracted with of ethyl acetate (3 x 300 mL) and the organic extracts were concentrated using a rotary evaporator. The product was then used directly without any purification. The residue was dissolved in 100 mL of methylene chloride and 50 mL of triethylamine (co-solvent) and treated with p-N,N-dimethylaminopyridine (100 mg, 0.8 mmol) followed by BOC anhydride (22.9 grams, 104 mmoles). The reaction mixture was stirred vigorously for 6 hours, quenched with 100 mL of brine, and extracted with 200 mL of ethyl acetate. The organic extracts were concentrated and then purified using flash chromatography (10 % ethyl acetate to hexanes isocratic solvent system) affording (S)-tert-butyl 2-oxo-3-(triisopropylsilyloxy)pyrrolidine-1-carboxylate (3-1) as an oil. ^{1}H NMR (400 MHz, D_3 acetonitrle) δ ppm 4.50 (t, J = 8.0 Hz, 1H), 3.70 (t, J = 8.2, 1H), 3.44-3.39 (m, 1H), 2.40-2.30 (m, 1H), 1.96-1.80 (m, 1H), 1.52 (s, 9H), 1.21-1.05 (m, 21H). LCMS observed *m/z* 737.5 major ion (calcd for 2M+Na, 737.5).

[000378] In step 3-2, a solution of 3-fluoro-1-bromo benzene (4.0 g, 22.9 mmol) in THF (10 mL) was cooled to -60 °C. To this solution n-BuLi in hexanes solution (1.6 M hexanes, 14.3 ml, 22.9 mmol) was added over 12 minutes allowing for a gradual temperature ramp (2 °C/minute) until a net internal temperature of -40 °C was obtained and all the n-BuLi was added. The reaction mixture was then allowed

to warm over a 30 minute period until an internal temperature of -22°C was reached, then the resulting solution (dark in color) was cooled to -45°C and then a solution of (S)-tert-butyl 2-oxo-3-(triisopropylsilyloxy)pyrrolidine-1-carboxylate (2.0 grams, 5.6 mmoles) in THF (10 mL) was added over 6 minutes (do not allow the internal temperature to exceed -40 °C during this addition event). The mixture was then allowed to warm to -20°C over a 35 minute period and the temperature was then held at -20°C for 2 hours. The reaction mixture was then quenched with cold saturated ammonium chloride aqueous solution (150 mL), warmed to room temperature and extracted with ethyl acetate (3 x 150 mL). The organic extracts were combined, concentrated using a rotary evaporator and purified using flash chromatography (5 % ethyl acetate in hexanes to 10 % ethyl acetate in hexanes over a 30 minute gradient) yielding the racemate of (3S)-tert-butyl 2-(3-fluorophenyl)-2-hydroxy-3-(triisopropylsilyloxy)pyrrolidine-1-carboxylate (3-2) as an oil. ^{1}H NMR (400 MHz, D_6 acetone) δ ppm 7.92-7.23 (m, 4H), 5.80 (br s, 1H), 5.10 (app t, *J* = 8.2, 1H), 3.20-2.95(m, 2H), 2.05-1.95 (m, 2H), 1.35 (s, 9H), 1.21-0.99 (m, 21H). LCMS observed *m/z* 737.5 major ion.

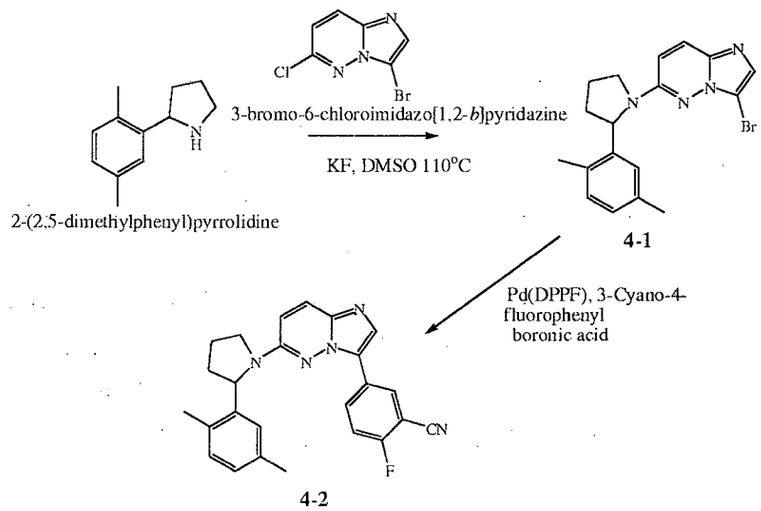
[000379] In step 3-3, a 4 N HCl dioxane (3 mL) solution was added to a solution of (3S)-tert-butyl 2-(3-fluorophenyl)-2-hydroxy-3-(triisopropylsilyloxy)pyrrolidine-1-carboxylate (1.1 g, 2.4 mmol) in methanol (30 mL)and stirred for 6 hours at room temperature. The reaction mixture was quenched with sodium bicarbonate (4 grams, 48 mmol) and the resulting slurry was treated with solid sodium borohydride (3 g, 79mmol) and stirred for 4 hours. 200 mL of brine was added to the reaction mixture and the solution was extracted with ethyl acetate (2 x 200 mL) and purified with reverse phase C-18 chromatography (water/acetonitrile 90:10 to 10:90 gradient) to afford (3S)-2-(3-fluorophenyl)-3-(triisopropylsilyloxy)pyrrolidine (3-3) as a dark red oil (mixture of diastereomers). ^{1}H NMR (400 MHz, D_3 acetonitrle) δ ppm 7.62-7.57 (m, 1H), 7.56-7.43 (m, 3H), 4.90-4.80 (m, 1H), 3.85-3.53 (m, 2H), 2.60-2.50 (m, 2H), 1.96-1.80 (m, 1H), 1.52 (s, 9H), 1.21-1.05 (m, 21H). LCMS observed *m/z* 338.2 major ion.

[000380] In step 3-4, KF (100 mg, 1.72 mmol) and 3-bromo-6-chloroimidazo[1,2-b]pyridazine (12-1) (700 mg, 3.0 mmol) were added to a solution of (3S)-2-(3-fluorophenyl)-3-(triisopropylsilyloxy)pyrrolidine (4-3) (700 g, 2.0 mmol) in 3 mL of DMSO. The resulting slurry was heated to 110 °C for 6 hours and then cooled, diluted with 8 mL of MeOH and purified using reverse phase C-18 chromatography (water/acetonitrile 90:10 to 10:90 gradient) to furnish (3S)-1-(3-bromoimidazo[1,2-b]pyridazin-6-yl)-2-(3-fluorophenyl)pyrrolidin-3-ol (3-4) as a solid (as a mixture of diastereomers). ^{1}H NMR (400 MHz, D_6 acetone) δ ppm 8.20 (app t, *J*= 6.5 Hz, 1H), 7.85-6.70 (m, 6H), 5.05 (app d, *J*= 5.5 Hz, 1H), 4.68 (app q, *J*= 7.5 Hz, 1H), 4.30 (br s, 1H), 4.01-3.92 (m, 1H), 3.82-3.70 (m, 1H), 2.35-1.87 (m, 2H). LCMS observed *m/z* 377.1, 379.1 major ion.

[000381] In step 3-5, in a microwave vessel sodium carbonate (105 mg, 1.0 mmol), 3-cyano phenylboronic acid (200 mg, 1.36 mmol) and Pd(DPPF)-dichloride catalyst (1,1'bis(diphenylsphosphino-ferrocene)-dichloropalladium (II) adduct with dichloromethane) (100 mg, 0.12 mmol) were added to a

solution (3S)-1-(3-bromoimidazo[1,2-b]pyridazin-6-yl)-2-(3-fluorophenyl)pyrrolidin-3-ol (1.40 g, 0.36 mmol) and 4 mL of 1,4-dioxane/water (3:1). This solution was then subjected to the following microwave conditions using a laboratory microwave instrument (conditons: 150 °C, 200 W max threshold, 20 atm. max pressure, 20 minute reaction time). The reaction mixture was purified directly with reverse phase C-18 HPLC (water/acetonitrile 90:10 to 10:90 gradient) to yield 3-(6-((3S)-2-(3-fluorophenyl)-3-hydroxypyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile (3-5) as a mixture of diastereomers. ^{1}H NMR (400 MHz, D_6 acetone) δ ppm 8.85 (br s, 1H), 8.40-8.03 (m, 3 H),7.90-7.22 (m, 5 H), 7.10 (app d, *J*= 5.5 Hz, 1H), 6.98 (app t, *J*= 4.5 Hz, 1H), 5.25 (app d, *J*= 4.5 Hz, 1H), 4.80 (app q, *J*= 7.5 Hz, 1H), 4.30 (br s, 1H), 3.82-3.75 (m, 1H), 3.3-3.55 (m, 1H), 2.42-2.34 (m, 1H), 2.25-2.12 (m, 1H). LCMS observed *m/z* 400.2.

Scheme 4



Example 4

5-(6-(3-(3-Fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)-1-(piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one

[000382] 5-(6-(2-(2,5-dimethylphenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-fluorobenzonitrile (5-2) was synthesized in two steps as shown in scheme 4.

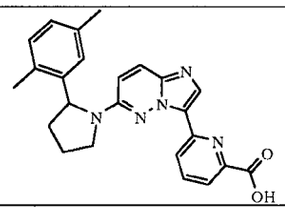
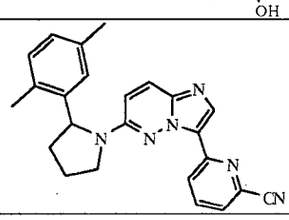
[000383] In step 4-1, potassium fluoride (58 mg, 1.0 mmol), and (3-bromo-6-chloroimidazo[1,2-b]pyridazine (12-1) (100 mg, 0.43 mmol) was added to a solution of 2-(2,5-dimethylphenyl)pyrrolidine (100 mg, 0.57 mmol) in 3 mL of DMSO. The reaction mixture was heated to130 °C and stirred for 6 hours at 130 °C. The reaction mixture was cooled to room temperature and purified using normal phase flash chromatography with ethyl acetate and hexanes (1:1) as a mobile phase to yield 3-bromo-6-(2-(2,5-dimethylphenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine (4-1) as its racemic mixture. ^{1}H NMR (400 MHz, D_3 acetonitrile) δ ppm 7.50 (app d, *J*= 9.5 Hz, 1H), 7.40 (br s, 1H), 7.08 (d, *J*= 6.5 Hz, 1H), 6.92 (d, *J*= 6.6

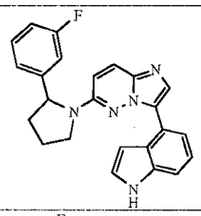
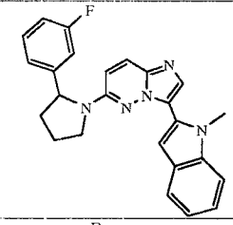
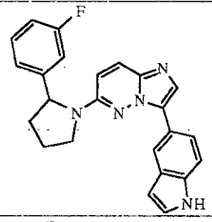
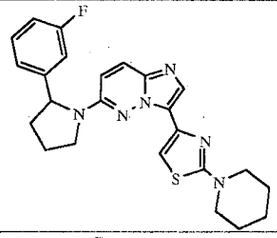
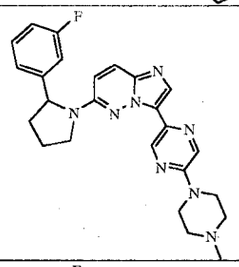
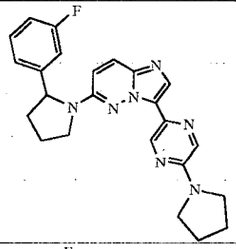
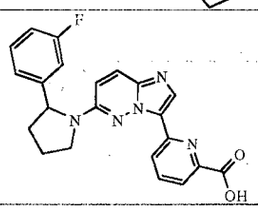
Hz, 1H), 6.82 (br s, 1H), 6.58 (br d, *J*= 9.5 Hz, 1H), 5.28 (br d, *J*= 5.0 Hz, 1H), 4.08-3.95 (m, 1H), 3.62 (app q, *J*= 6.4 Hz, 1H), 3.30 (s,1H), 2.51-2.42 (m, 1H), 2.24 (br s, 6H), 2.17-2.04 (m, 2H) . LCMS observed *m/z* 371.1, 373.1 major ion.

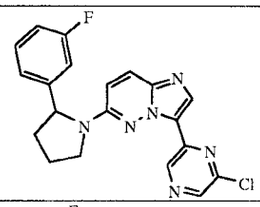
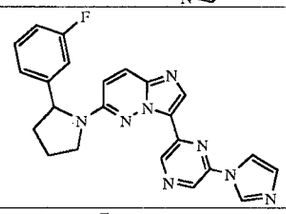
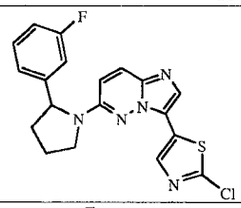
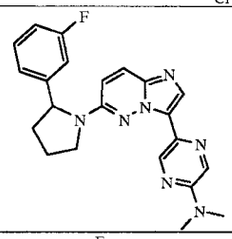
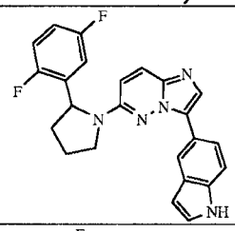
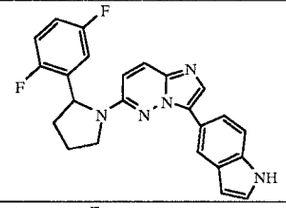
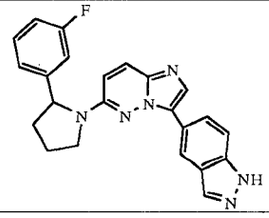
[000384] In step 4-2, sodium carbonate (30 mg, 0.30 mmol), 3-cyano-4-fluoro phenylboronic acid (30 mg, 0.24 mmol) and Pd(DPPF)-dichloride catalyst (1,1'bis(diphenylsphosphino-ferrocene)-dichloropalladium (II) adduct with dichloromethane) (10 mg, 0.012 mmol) was added into in a microwave vessel containing a solution of 3-bromo-6-(2-(2,5-dimethylphenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine (50 mg, 0.13 mmol) and 2.5 mL of 1,4-dioxane/water (3:1). The reaction mixture was subjected to the following microwave conditions using a laboratory microwave instrument (conditons: 150 °C, 200 W max threshhold, 20 atm. Max pressure, 20 minute reaction time). The resulting solution was purified using preparatory LC/MS (reverse phase C-18 chromatography) to yield 5-(6-(2-(2,5-dimethylphenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-fluorobenzonitrile (4-2). ^{1}H NMR (400 MHz, D_3 acetonitrile) δ ppm 8.50-8.10 (m, 2H), 7.80 (br s, 1H), 7.50 (app d, *J*= 8.5 Hz, 1H), 7.20 (app t, *J*= 6.5 Hz, 1H), 7.06 (d, *J*= 6.5 Hz, 1H), 6.93 (d, *J*= 6.6 Hz, 1H), 6.81 (br s, 1H), 6.60 (br s, 1H), 5.22 (app dd, *J*= 6.2, 2.1 Hz, 1H), 4.05-4.00 (m, 1H), 3.76 (app q, *J*= 6.4 Hz, 1H), 3.36 (app d, *J*= 2.2 Hz, 1H), 2.58-2.43 (m, 1H), 2.24 (br s, 6H), 2.19-2.08 (m, 2H) . LCMS observed *m/z* 412.2.

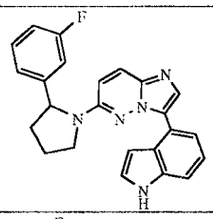
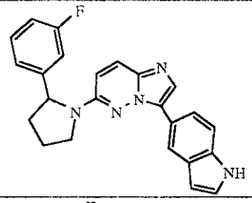
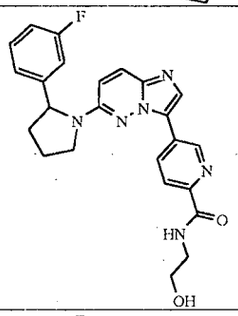
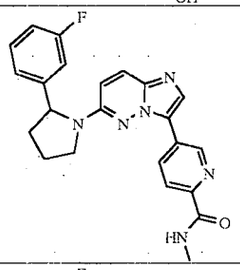
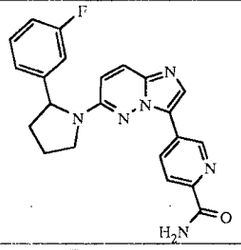
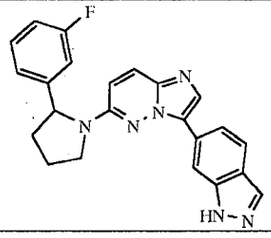
[000385] By repeating the procedures described in the above examples, using appropriate starting materials, the following compounds of Formula I, as identified in Table 3, were obtained.

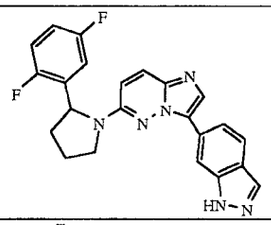
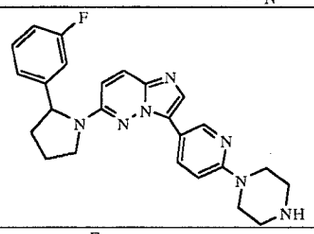
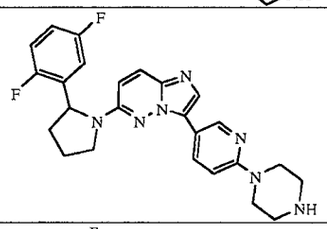
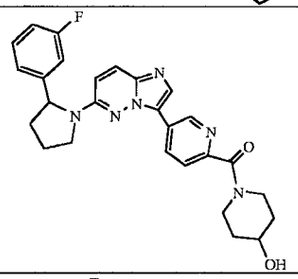
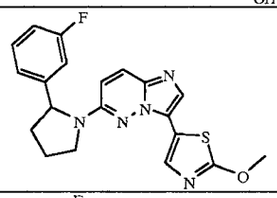
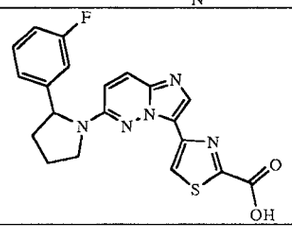
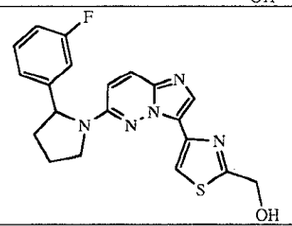
Table 3

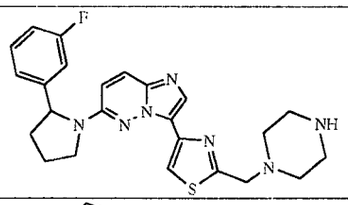
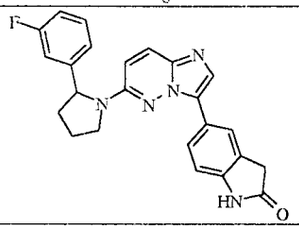
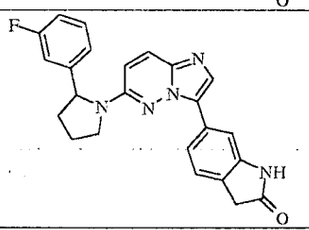
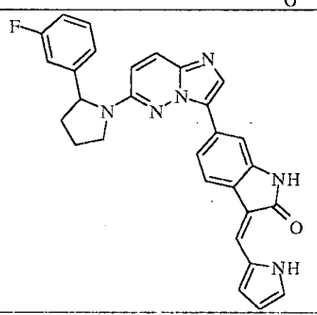
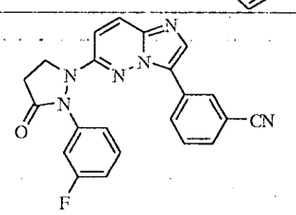
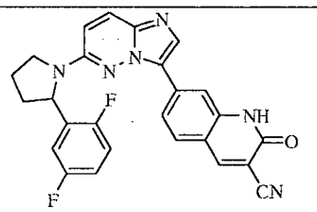
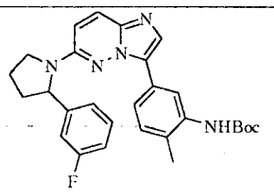
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
1		*m/z* 414.2 (M+1)
2		*m/z* 395.2 (M+1)

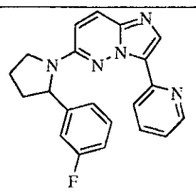
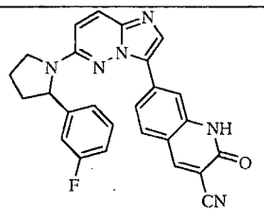
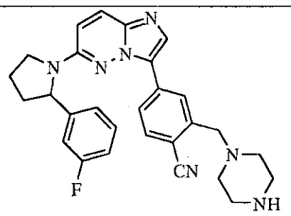
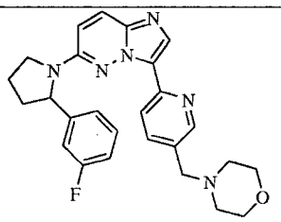
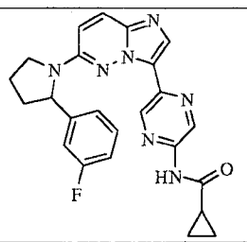
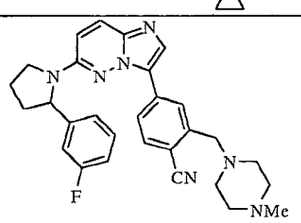
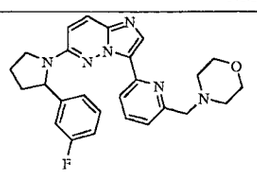
3		*m/z* 398.2 (M+1)
4		*m/z* 412.2 (M+1)
5		*m/z* 398.2 (M+1)
6		*m/z* 449.2 (M+1)
7		*m/z* 459.2 (M+1)
8		*m/z* 430.2 (M+1)
9		*m/z* 404.2 (M+1)

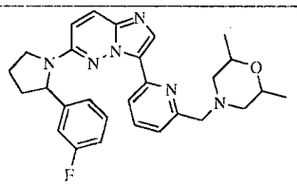
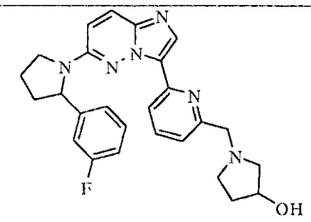
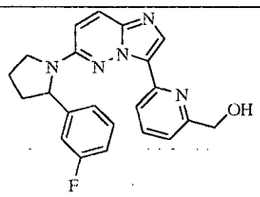
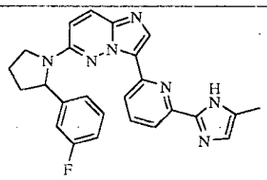
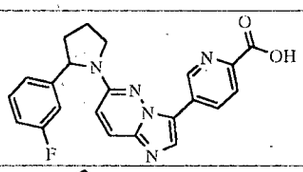
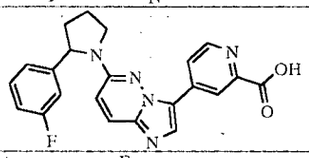
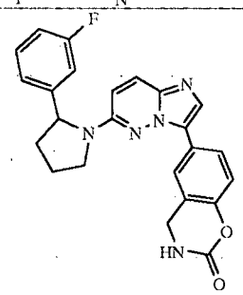
10		*m/z* 395.2 (M+1)
11		*m/z* 427.2 (M+1)
12		*m/z* 400.6 (M+1)
13		*m/z* 404.2 (M+1)
14		*m/z* 416.2 (M+1)
15		*m/z* 416.2 (M+1)
16		*m/z* 399.2 (M+1)

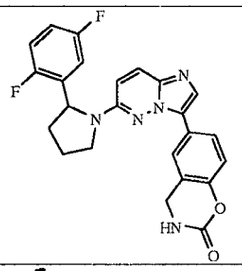
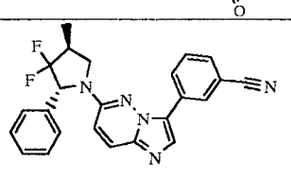
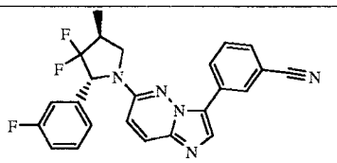
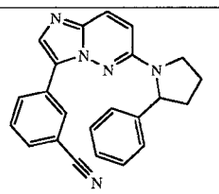
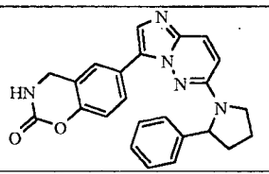
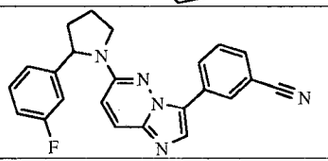
17		*m/z* 398.2 (M+1)
18		*m/z* 398.2 (M+1)
19		*m/z* 447.2 (M+1)
20		*m/z* 417.2 (M+1)
21		*m/z* 404.2 (M+1)
22		*m/z* 399.2 (M+1)

23		*m/z* 417.2 (M+1)
24		*m/z* 444.5 (M+1)
25		*m/z* 462.2 (M+1)
26		*m/z* 487.3 (M+1)
27		*m/z* 396.2 (M+1)
28		*m/z* 410.2 (M+1)
29		*m/z* 396.2 (M+1)

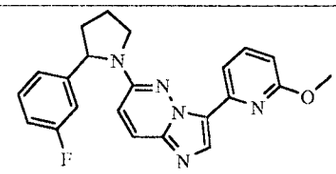
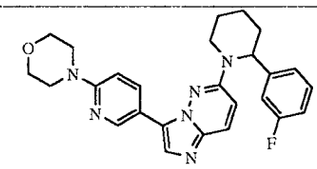
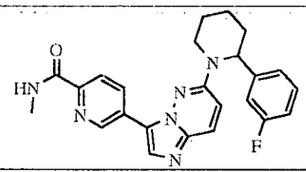
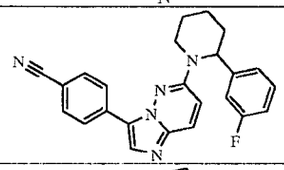
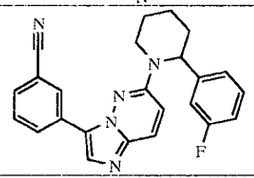
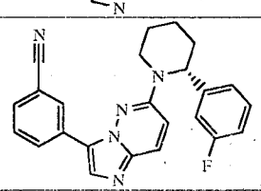
30		*m/z* 464.2 (M+1)
31		*m/z* 414 (M+1)
32		^{1}H NMR DMSO-d6 (ppm) 10.64 (s, 1H), 8.31 (m, 1H), 8.05 (m, 1H), 7.64 (m, 1H), 7.35 (m, 2H), 7.13 (m ,5H), 5.23 (m 1H), 4.01 (m, 2H), 3.69 (m, 1H), 3.56 (s, 2H), 2.05 (m, 2H), 1.91 (m, 1H); *m/z* 414 (M+1)
33		*m/z* 491 (M+1)
34		MS *m/z* 399 (M+1)
35		MS *m/z* 469 (M+1)
36		MS *m/z* 488 (M+1)

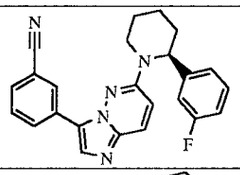
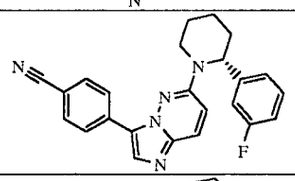
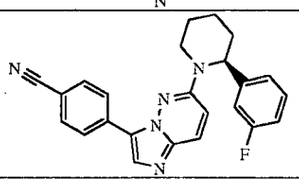
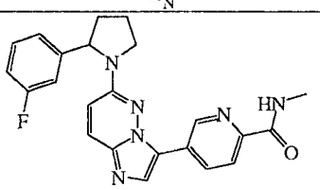
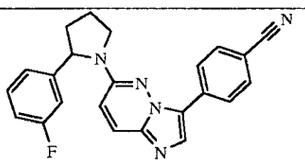
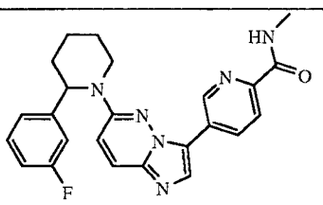
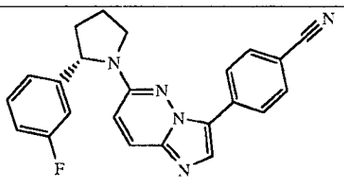
37		MS *m/z* 360 (M+1)
38		MS *m/z* 451 (M+1)
39		MS *m/z* 482 (M+1)
40		MS *m/z* 459 (M+1)
41		MS *m/z* 444 (M+1)
42		MS *m/z* 496 (M+1)
43		MS *m/z* 459 (M+1)

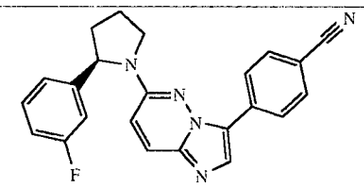
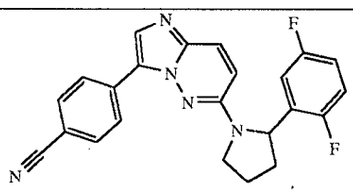
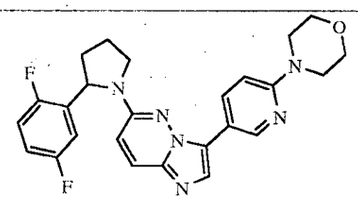
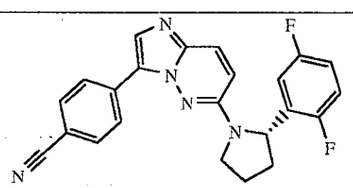
44		MS *m/z* 487 (M+1)
45		MS *m/z* 459 (M+1)
46		MS *m/z* 389 (M+1)
47		MS m/z 440 (M+1)
48		*m/z* 404.2 (M+1)
49		*m/z* 404.2 (M+1)
50		1H NMR (DMSO-d6): δ 8.02 (s, 1 H), 7.90 (s, 1 H), 7.88 (s, 1 H), 7.86 (s, 1 H), 7.37-7.40 (m, 1 H), 7.14 (d, 2 H), 7.05 (t, 1 H), 6.95 (d, 1 H), 6.81 (d, 1 H), 5.18 (d, 1 H), 4.40-4.45 (m, 1 H), 4.30-4.40 (m, 1 H), 3.95-3.99 (m, 1H), 3.62-3.66 (m, 1H), ; 2.43-2.49 (m, 1H), 1.95-2.05 (m, 2H), 1.85-1.90 (m, 1H) *m/z* 430.4 (M+1)

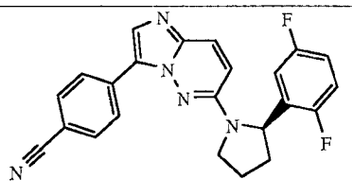
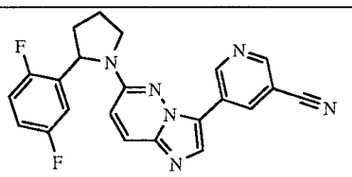
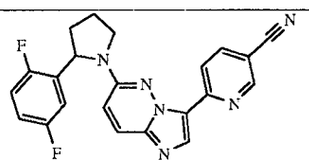
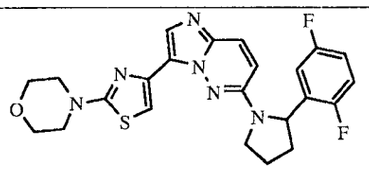
51		*m/z* 448.4 (M+1)
52		1H NMR (DMSO-d6): d 8.49 (s, 1 H), 8.18-8.24 (m, 1 H), 8.16 (s, 1 H), 8.00 (d, 1 H), 7.73 (d, 1 H), 7.56 (t, 1 H), 7.49 (d, 2 H), 7.40 (t, 2 H), 7.32 (t, 1 H), 6.88-6.96 (m, 1 H), 5.43 (d, 1 H), 4.37 (t, 1 H), 3.40 (t, 1H), 2.76-2.94 (m, 1H), 1.17 (d, 3H) *m/z* 416.4 (M+1)
53		1H NMR (DMSO-d6): 8.55 (s, 1 H), 8.18-8.25 (m, 1 H), 8.16 (s, 1 H), 8.00 (d, 1 H), 7.74 (d, 1 H), 7.55 (t, 1 H), 7.42-7.49 (m, 1 H), 7.33-7.39 (m, 2 H), 7.11-7.19 (m, 1 H), 6.88-6.98 (m, 1 H), 5.47 (d, 1 H), 4.38 (t, 1 H), 3.86 (t, 1H), 2.78-2.94 (m, 1H), 1.17 (d, 3H) *m/z* 434.4 (M+1)
54		H NMR (DMSO-d6) d 855 (s, 1 H), 8.20-8.32 (bs, 1 H), 8.12 (s, 1H), 7.89 (d, 1 H), 7.71 (d, 1 H), 7.54 (t, 1 H), 7.26-7.36 (m, 4 H), 7.18-7.24 (m, 1 H), 6.76-6.91 (bs, 1 H), 5.15-5.21 (m, 1 H), 3.94-4.02 (m, 1 H), 3.66-3.72 (m, 1 H), 2.45-2.50 (m, 1 H), 2.01-2.08 (m, 2 H), 1.82-1.90 (m, 1 H) *m/z* 366.4 (M+1)
55		*m/z* 412.5 (M+1)
56		*m/z* 384.4 (M+1)

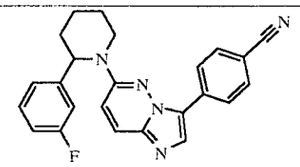
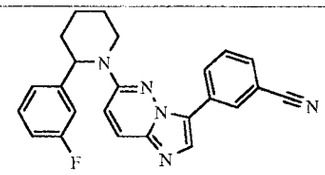
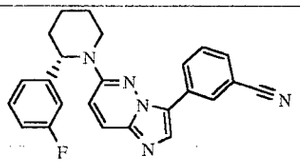
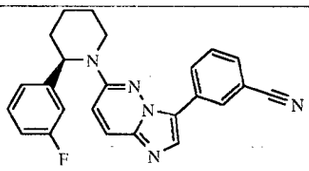
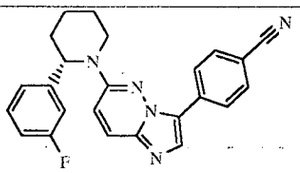
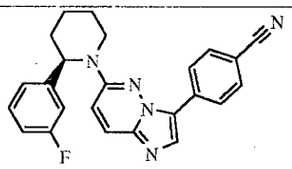
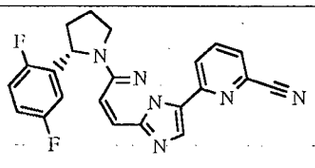
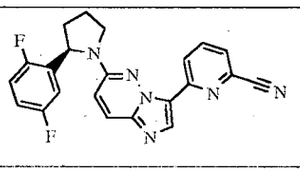
69

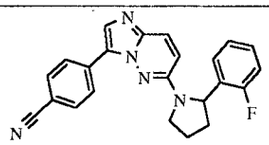
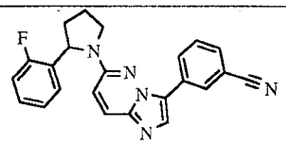
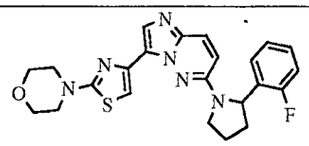
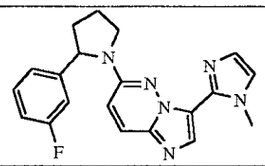
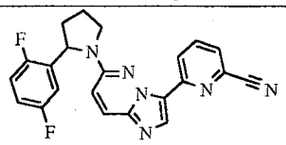
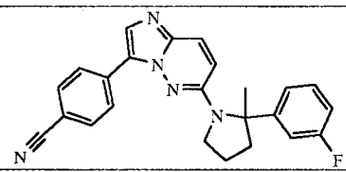
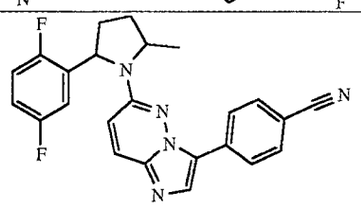
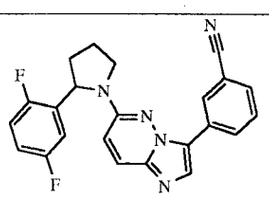
57		1H NMR (DMSO-d6) 8.14 (s, 1 H), 7.91 (s, 1 H), 7.58-7.64 (m, 2 H), 7.53-7.57 (m, 1 H), 7.35-7.41 (m, 1 H), 7.15-7.17 (m, 2 H), 7.01-7.05 (m, 1 H), 6.68 (d, 1 H), 5.16-5.19 (q, 1 H), 3.98-4.02 (m, 1 H), 3.91 (s, 3 H), 3.65-3.71 (m, 1 H), 2.44-2.49 (m, 1 H), 2.01-2.07 (m, 2 H), 1.85-1.90 (m, 1 H) *m/z* 390.4 (M+1)
58		HNMR (DMSO-d6, 400MHz) 8.725 (d, J= 0.005, 1H) 8.374 (s, 1H) 8.195 (d, J = 0.025, 1H) 8.074 (dd, J = 0.023, 0.006, 1H) 7.705 (d, J = 0.026, 1H) 7.406 (q, J = 0.02, 1H) 7.149 (s, 1H) 7.129 (s, 1H) 7.082 (dt, J = 0.015, 0.005, 1H) 6.973 (d, J = 0.023, 1H) 5.561 (t, J = 0.01, 1H) 4.270 (d, J = 0.033, 1H) 3.725 (t, J = 0.011, 4H) 3.561 (t, J = 0.013, 4H) 3.317 (dt, J = 0.035, 0.01, 1H) 2.265 (m, 1H) 20.39 (m, 1H) 1.782 (m, 1H) 1.649 (m, 2H) 1.455 (m, 1H) *m/z* 459.2 (M+1)
59		*m/z* 431.2 (M+1)
60		*m/z* 398.2 (M+1)
61		*m/z* 398.2 (M+1)
62		*m/z* 398.2 (M+1)

63		*m/z* 398.2 (M+1)
64		*m/z* 398.2 (M+1)
65		*m/z* 398.2 (M+1)
66		HNMR (DMSO-d6, 400MHz) 9.198 (br.s, 1H) 8.790 (ds, J = 0.011, 1H) 8.504 (s, 1H) 8.102 (d, J = 0.025, 1H) 8.008 (br.s, 1H) 7.377 (q, J = 0.019, 1H) 7.166 (d, J = 0.019) 7.166 (m, 3H) 7.083 (dt, J = 0.019, 0.004, 1H) 5.192 (d, J = 0.017, 1H)4.011 (m, 1H) 3.695 (q, J = 0.025, 1H) 2.868 (d, J = 0.012, 3H) 2.451 (m, 1H) 2.056 (m, 2H), 1.898 (m, 1H) *m/z* 417.5 (M+1)
67		*m/z* 384.4 (M+1)
68		*m/z* 431.5 (M+1)
69		HNMR (DMSO-d6, 400MHz) 8.205 (br.s, 2H) 7.994 (d, J = 0.025, 1H) 7.815 (d, J = 0.019, 2H) 7.486 (q, J = 0.021, 1H) 7.222 (m, 2H) 7.108 (dt, J = 0.023, 0.006, 1H) 6.959 (br.s, 1H) 5.209 (dd, J = 0.021, 0.007, 1H) 4.048 (p, J = 0.014, 1H) 3.719 (q, J = 0.02, 1H) 2.513 (m, 1H),

		2.092 (m, 2H) 1.919 (m, 1H) *m/z* 384.4 (M+1)
70		HNMR (DMSO-d6, 400MHz) 8.084 (br.s, 2H) 7.875 (d, J = 0.024, 1H) 7.697 (d, J = 0.02, 2H) 7.364 (q, J = 0.02, 1H) 7.100 (m, 2H) 6.985 (dt, J = 0.023, 0.006, 2H) 6.841 (br.s, 1H)5.091 (dd, J = 0.02, 0.006, 1H) 3.928 (p, J = 0.014 1H) 3.600 (q, J = 0.021, 1H) 2.370 (m, 1H) 1.971 (m, 2H) 1.797 (m, 1H) *m/z* 384.4 (M+1)
71		*m/z* 402.4 (M+1)
72		HNMR (DMSO-d6, 400MHz) 8.572 (br.s, 1H) 7.739 (m, 3H) 7.306 (m, 1H) 7.056 (m, 1H)7.056 (m, 1H) 6.954 (m, 1H) 6.739 (s, 1H) 6.638 (m, 1H) 5.203 (d, J = 0.016, 1H) 3.916 (m, 1H) 3.837 (m, 1H) 3.667 (m, 4H) 3.540 (m, 1H) 3.425 (m, 4H) 2.391 (m, 1H) 2.009 (m, 2H) 1.830 (m, 1H) *m/z* 463.5 (M+1)
73		HNMR (DMSO-d6, 400MHz) 8.094 (s, 1H) 7.998 (br.s, 2H) 7.917 (d, J = 0.024, 1H) 7.660 (d, J = 0.021 2H) 7.423 (dq, J = 0.024, 0.011, 1H)7.061 (m, 1H) 6.992 (m, 1H) 6.925 (br.s, 1H) 5.248 (d, J = 0.019, 1H) 3.962 (m, 1H) 3.561 (q, J = 0.018, 1H) 2.382 (m, 1H) 1.998 (m, 2H) 1.830 (m, 1H)

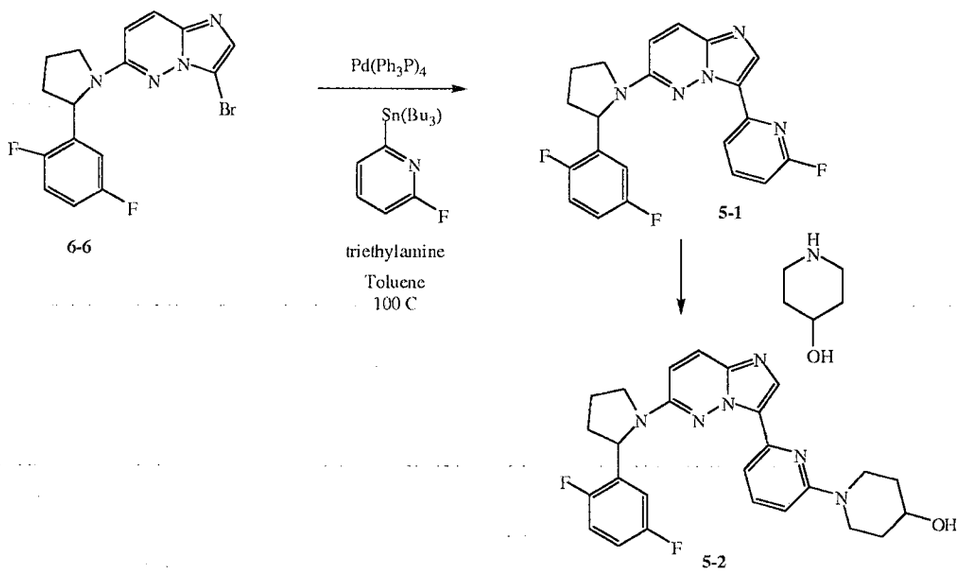
		m/z 402.4 (M+1)
74		HNMR (DMSO-d6, 400MHz) 8.091 (s, (1H) 7.994 (br.s, 2H) 7.913 (d, J = 0.025, 1H) 7.655 (d, J = 0.02, 1H) 7.421 (dq, J = 0.021, 0.011, 1H) 7.059 (m, 1H) 6.989 (m, 1H) 6.925 (br.s, 1H) 5.242 (d, J = 0.019, 1H) 3.959 (m, 1H) 3.556 (q, J = 0.018, 1H) 2.390 (m, 1H) 1.997 (m, 2H) 1.819 (m, 1H) *m/z* 402.4 (M+1)
75		*m/z* 403.4 (M+1)
76		*m/z* 403.4 (M+1)
77		HNMR (DMSO-d6, 400MHz) 7.854 (d, J= 0.024, 1H) 7.710 (s, 1H) 7.248 (m, 1H) 7.072 (m, 1H) 6.979 (m, 1H) 6.801 (m, 1H), 6.694 (m, 1H) 5.274 (d, J = 0.019, 1H) 3.948 (dt, J = 0.025, 0.007, 1H) 3.658 (t, 0.011, 4H), 3.572 (q, J = 0.024, 1H) 3.359 (t, J = 0.012, 3H) 2.007 (m, 3H) 1.285 (s, 1H) 1.164 (s, 1H) *m/z* 469.5 (M+1)

78		*m/z* 398.4 (M+1)
79		*m/z* 398.4 (M+1)
80		*m/z* 398.4 (M+1)
81		*m/z* 398.4 (M+1)
82		*m/z* 398.4 (M+1)
83		*m/z* 398.4 (M+1)
84		*m/z* 403.4 (M+1)
85		*m/z* 403.4 (M+1)

86		*m/z* 384.4 (M+1)
87		*m/z* 384.4 (M+1)
88		*m/z* 451.5 (M+1)
89		*m/z* 363.4 (M+1)
90		*m/z* 403.4 (M+1)
91		*m/z* 398.4 (M+1)
92		8.166 (s, 1H) 8.019 (s, 1H) 7.998 (d, J = 0.01, 1H) 7.963 (s, 1H) 7.719 (d, J = 0.021, 2H) 7.514 (dq, J = 0.024, 0.011, 1H) 7.143 (m, 1H) 6.990 (m, 2H) 5.199 (t, J = 0.02, 1H) 4.338 (d sextet, J = 0.017, 0.006, 1H) 2.550 (m, 1H) 2.223 (m, 1H) 1.944 (m, 1H) 1.768 (m, 1H) 1.497 (d, J = 0.016, 3H) *m/z* 416.4 (M+1)
93		8.327 (br s, 1H) 8.123 (s, 2H) 7.938 (d, J = 0.025, 1H) 7.678 (d, J = 0.020, 1H) 7.423 (t, J = 0.020, 1H) 7.272 (m, 1H) 7.045 (m, 1H) 6.964 (m, 2H) 5.275 (d, J = 0.019, 1H) 3.967 (dt, J = 0.024, 0.006, 1H) 3.564 (q, J = 0.023, 2H) 1.998 (m, 3H)

		m/z 402.4 (M+1)

Scheme 5



Example 5

1-(6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl) pyridin-2-yl)piperidin-4-ol

[000386] 1-(6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol (5-2) was synthesized in two steps as shown in scheme 5.

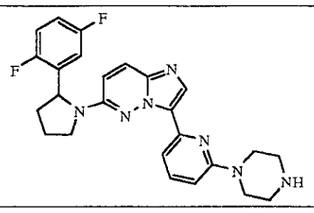
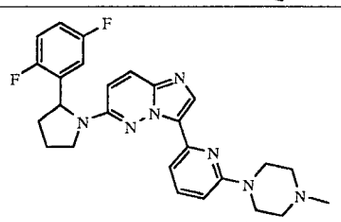
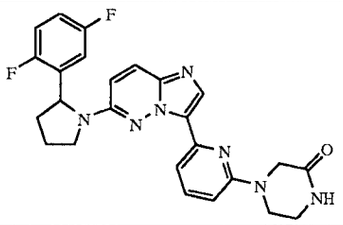
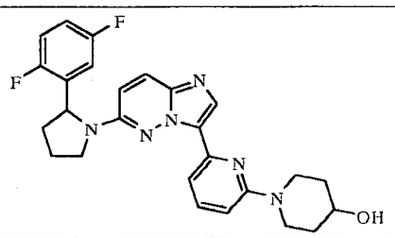
[000387] In step 5-1, triethylamine (0.045 mL, 0.29 mmol), tetrakis(triphenylphospine)palladium (0) (12 mg, 0.01 mmol), and 6-fluoro-2(tributylstannyl)pyridine (80 mg, 0.201 mmol) were added to a solution of 3-bromo-6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine (6-6) (53 mg, 0.13 mmol) in 3 mL of toluene. The reaction mixture was heated to 100 °C and stirred for 6 hours at 100 °C. The reaction mixture was then cooled to room temperature and purified using flash chromatography (ethyl acetate and hexanes (1:1)) giving 6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(6-fluoropyridin-2-yl)imidazo[1,2-b]pyridazine (5-1). ^{1}H NMR (400 MHz, D_3 acetonitrile) δ ppm 8.35-8.17 (m, 2H), 8.02-7.83 (m, 1H), 7.48-7.22 (m, 3H), 7.15-6.92 (m, 3H), 5.42 (br d, *J*= 5.8 Hz, 1H), 4.12-3.99 (m, 1H), 3.81-3.72 (m, 1H), 2.70-2.56 (m, 1H), 2.30-2.06 (m, 3H) . LCMS observed *m/z* 396.1

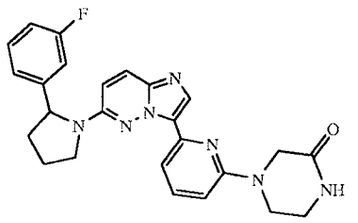
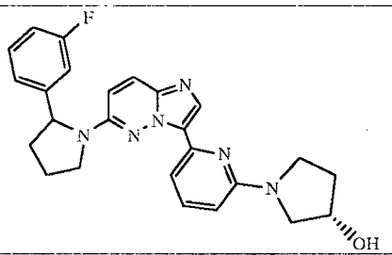
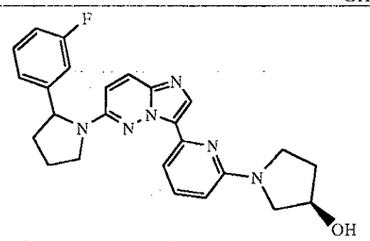
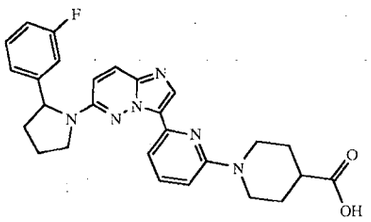
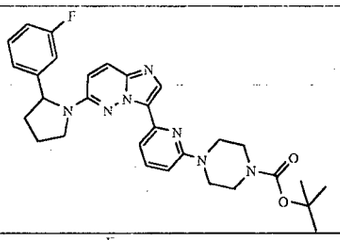
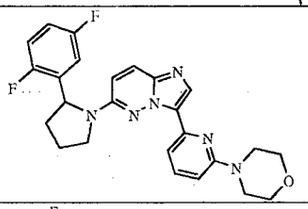
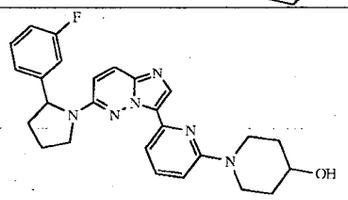
[000388] In step 5-2, 4-hydroxy-piperidine (30 mg, 0.30 mmol) was added to a mixture of 6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(6-fluoropyridin-2-yl)imidazo[1,2-b]pyridazine (40 mg, 0.13 mmol), 12

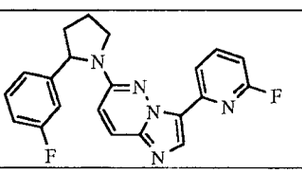
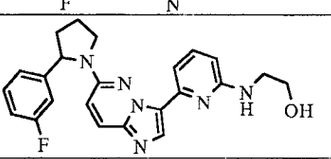
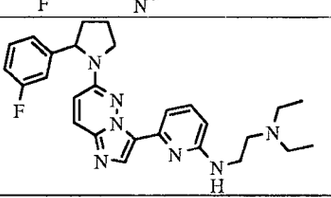
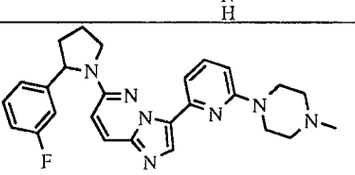
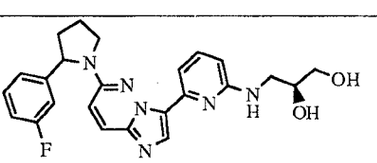
mg KF (0.30 mmol) in 1.5 mL of DMSO. The resulting mixture was heated to110°C and stirred for 8 hours at 110°C. The product was then purified using mass triggered preparatory LC/MS giving 1-(6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol (5-2). ^{1}H NMR (400 MHz, D_3 acetonitrile) δ ppm 8.35 (br s, 1H), 8.22 (app q, *J*= 6.1 Hz, 2H), 7.58 (br s, 1H), 7.42-7.02 (m, 4H), 6.82 (app d, *J*= 6.5 Hz, 1H), 5.42 (dd, *J*= 5.2, 1.4 Hz, 1H), 4.25-4.00 (m, 3H), 3.88-3.82 (m, 1H), 3.76 (app q, *J*= 6.4 Hz, 1H), 3.15 (app dd, *J*= 4.7, 2.2 Hz, 2H), 2.49-2.42 (m, 2H), 2.09-2.01 (m, 3H), 1.88-1.80 (m, 2H), 1.44 (app q, *J*= 7.4 Hz, 2H). LCMS observed *m/z* 477.2

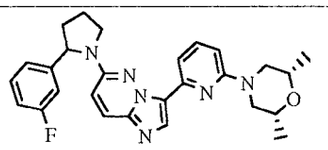
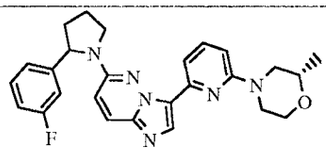
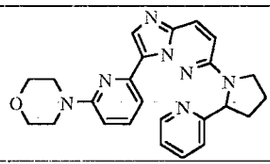
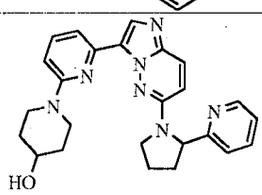
[000389] By repeating the procedures described in the above examples, using appropriate starting materials, the following compounds of Formula (I), as identified in Table 4, were obtained.

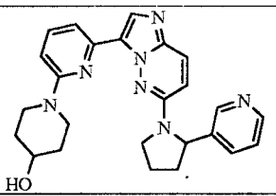
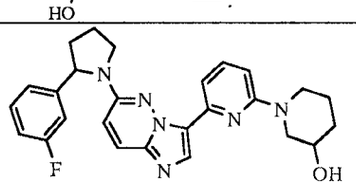
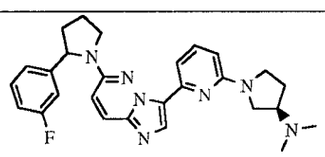
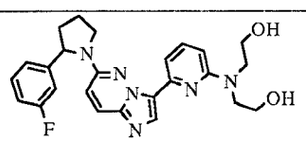
Table 4

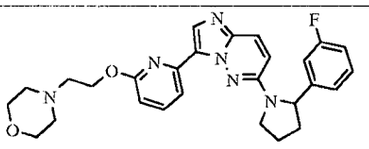
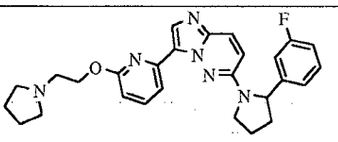
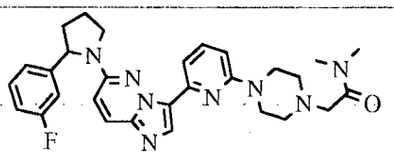
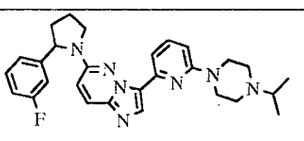
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
1		*m/z* 462.2 (M+1)
2		*m/z* 476.3 (M+1)
3		*m/z* 476.3 (M+1)
4		*m/z* 477.3 (M+1)

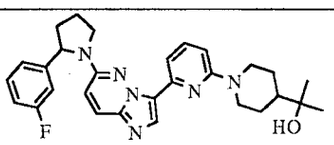
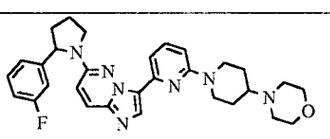
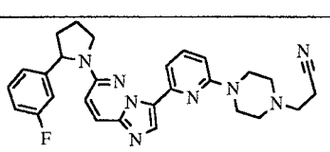
5		*m/z* 458.2 (M+1)
6		*m/z* 445.2 (M+1)
7		*m/z* 445.2 (M+1)
8		*m/z* 487.2 (M+1)
9		*m/z* 544.3 (M+1)
10		*m/z* 463.2 (M+1)
11		1H NMR (DMSO-d6) 8.04 (s, 1 H), 7.88 (d, 1 H), 7.40-7.60 (m, 2 H), 7.37 (q, 1 H), 7.13-7.17 (m, 2 H), 7.00-7.05 (m, 1 H), 6.75-6.85 (bs, 1 H), 6.73 (d, 1 H), 5.15-5.17 (m, 1 H), 4.67 (d, 1 H), 4.04-4.10 (m, 2 H), 3.96-4.01 (m, 1 H),

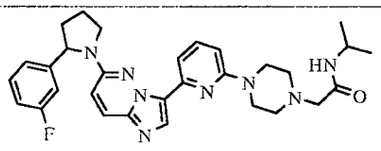
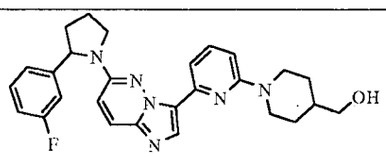
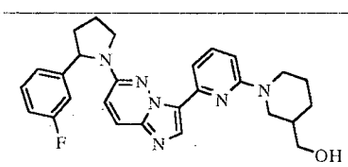
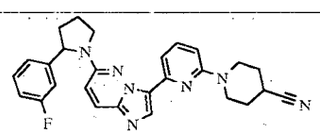
		3.64-3.71 (m, 2 H), 3.05-3.11 (m, 2 H), 2.00-2.06 (m, 2 H), 1.84-1.89 (m, 1 H), 1.77-1.82 (m, 2 H), 1.33-1.40 (m, 2 H) *m/z* 473.2 (M+1)
12		*m/z* 378.4 (M+1)
13		*m/z* 419.5 (M+1)
14		*m/z* 474.6 (M+1)
15		1H NMR (DMSO-d6) 8.10 (s, 1 H), 7.88 (d, 1 H), 7.46-7.66 (m, 2 H), 7.36-7.40 (m, 1 H), 7.12-7.18 (m, 2 H), 7.00-7.06 (m, 1 H), 6.80-6.90 (m, 1 H), 6.78 (d, 1 H), 5.14-5.18 (m, 1 H), 4.20 (d, 1 H), 4.11 (d, 1 H), 3.96-4.02 (m, 1 H), 3.50-3.90 (m, 4 H), 3.64-3.70 (m, 1 H), 3.32 (s, 3 H), 2.70-3.00 (m, 4 H), 2.45-2.50 (m, 1 H), 2.00-2.08 (m, 2 H), 1.84-1.91 (m, 1 H) *m/z* 458.5 (M+1)
16		1H NMR (DMSO-d6) 8.03 (s, 1 H), 7.88 (d, 1 H), 7.26-7.44 (m, 3 H), 7.12-7.18 (m, 2 H), 7.01-7.06 (m, 1 H), 6.75-6.85 (m, 1 H), 6.50-6.56 (m, 1 H), 6.43 (d, 1 H), 5.14-5.18 (m, 1 H), 5.00-5.06 (bs, 1 H), 4.58-4.68 (m, 1 H), 3.95-4.05 (m, 1 H), 3.62-3.70 (m, 2 H), 3.42-3.50 (m, 1 H), 3.36-3.38 (m, 2 H), 3.18-3.26 (m, 1 H), 2.45-2.50 (m, 1 H), 2.00-2.08 (m, 2 H), 1.82-1.90 (m, 1 H) *m/z* 449.5 (M+1)

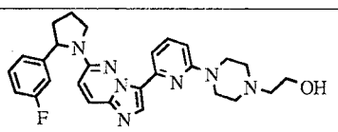
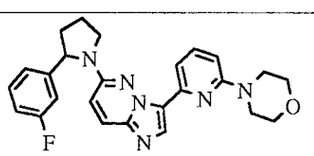
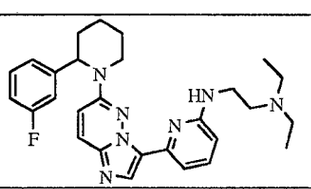
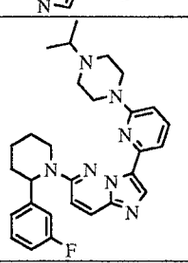
17		1H NMR (DMSO-d6) 8.10 (s, 1 H), 7.89 (d, 1 H), 7.42-7.60 (m, 2 H), 7.34-7.42 (m, 1 H), 7.12-7.18 (m, 2 H), 6.98-7.06 (m, 1 H), 6.76-6.86 (m, 1 H), 6.74 (d, 1 H), 5.14-5.19 (m, 1 H), 4.21 (d, 2 H), 3.96-4.02 (m, 1 H) , 3.64-3.70 (m, 3 H), 2.45-2.50 (m, 1 H), 2.35-2.43 (m, 2 H), 1.98-2.08 (m, 2 H), 1.82-1.90 (m, 1 H), 1.18 (m, 6 H) *m/z* 473.6 (M+1)
18		1H NMR (DMSO-d6) 8.09 (s, 1 H), 7.89 (d, 1 H), 7.42-7.64 (m, 2 H), 7.33-7.42 (m, 1 H), 7.12-7.18 (m, 2 H), 6.98-7.06 (m, 1 H), 6.76-6.86 (m, 1 H), 6.73 (d, 1 H), 5.14-5.18 (m, 1 H), 4.20 (d, 1 H), 4.11 (d, 1 H), 3.95-4.05 (m, 1 H), 3.62-3.70 (m, 1 H), 3.50-3.62 (m, 2 H), 3.36-3.38 (m, 2 H), 2.74-2.84 (m, 1 H), 2.45-2.50 (m, 1 H), 1.98-2.07 (m, 2 H), 1.82-1.91 (m, 1 H), 1.18 (m, 3 H) *m/z* 459.5 (M+1)
19		*m/z* 428.5 (M+1)
20		1H NMR (DMSO-d6) 8.57 (d, 1 H), 8.03 (s, 1 H), 7.87 (d, 1 H), 7.67-7.71 (m, 1 H), 7.36-7.48 (bs, 2 H), 7.29 (d, 1 H), 7.20-7.23 (m, 1 H), 6.78-6.88 (bs, 1 H), 6.71 (d, 1H), 5.16-5.19 (q, 1 H), 4.65-4.68 (d, 1 H), 4.04-4.09 (m, 2H), 3.94-3.98 (m, 1 H), 3.65-3.73 (m, 2 H), 3.04-3.11 (m, 2 H), 2.45-2.48 (m, 1 H), 2.03-2.08 (m, 2 H), 1.95-2.01 (m, 1 H), 1.76-1.82 (m, 2 H), 1.33-1.40 (m, 2 H) *m/z* 442.5 (M+1)

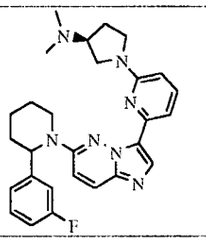
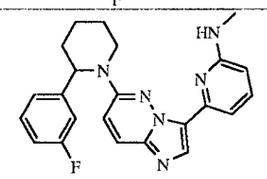
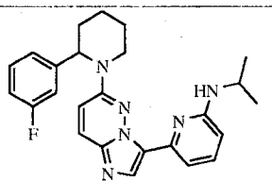
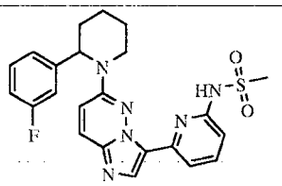
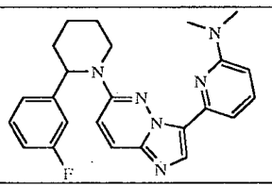
21		*m/z* 442.5 (M+1)
22		1H NMR (DMSO-d6) 8.06 (s, 1 H), 7.88 (d, 1 H), 7.40-7.50 (m, 2 H), 7.35-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.01-7.05 (m, 1 H), 6.75-6.85 (bs, 1 H), 6.69 (d, 1 H), 5.14-5.18 (q, 1 H), 4.83 (t, 1 H), 4.24-4.29 (m, 1H), 3.95-4.05 (m, 2 H), 3.63-3.70 (m, 1 H), 3.44-3.53 (m, 1 H), 2.87-2.93 (m,1 H), 2.67-2.73 (q, 1 H), 2.45-2.50 (m, 1 H), 2.00-2.06 (m, 2 H), 1.84-1.94 (m, 2 H), 1.70-1.76 (m, 1 H), 1.33-1.40 (m, 2 H) *m/z* 459.5 (M+1)
23		1H NMR (DMSO-d6) 8.07 (s, 1 H), 7.87 (d, 1 H), 7.32-7.60 (m, 3 H), 7.11-7.19 (m, 2 H), 7.00-7.05 (m, 1 H), 6.75-6.85 (bs, 1 H), 6.36 (d, 1 H), 5.15-5.18 (m, 1 H), 3.96-4.01 (m, 1 H), 3.60-3.75 (m, 3 H), 3.33-3.37 (m, 1 H), 3.10-3.15 (m, 1 H), 2.73-2.80 (m, 1 H), 2.45-2.50 (m, 1 H), 2.11-2.18 (m, 1 H), 2.00-2.06 (m, 2 H), 1.84-1.90 (m, 1 H), 1.76-1.82 (m, 1 H) *m/z* 472.6 (M+1)
24		1H NMR (DMSO-d6) 8.58 (d, 1 H), 8.41-8.43 (q, 1H), 8.02 (s, 1 H), 7.89 (d, 1 H), 7.68-7.71 (m, 1 H), 7.39-7.45 (m, 2 H), 7.32-7.35 (q, 1 H), 6.82-6.90 (bs, 1 H), 6.72 (d, 1H), 5.19-5.23 (q, 1 H), 4.67 (d, 1 H), 4.03-4.09 (m, 2 H), 3.97-4.02 (m, 1 H), 3.65-3.71 (m, 2 H), 3.05-3.10 (m, 2 H), 2.51-2.53 (m, 1 H), 2.01-2.09 (m, 2 H), 1.85-1.91 (m, 1 H), 1.76-1.82 (m, 2 H), 1.31-1.40 (m, 2 H) *m/z* 463.5 (M+1)

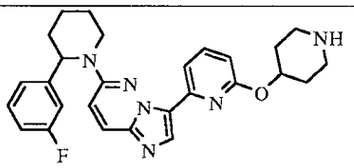
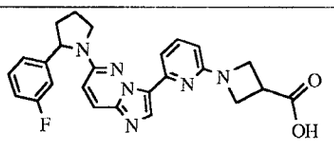
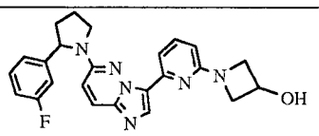
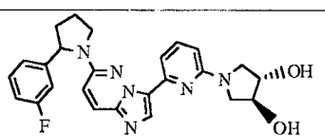
25		1H NMR (DMSO-d6) 8.58 (d, 1 H), 8.41-8.43 (q, 1H), 8.02 (s, 1 H), 7.89 (d, 1 H), 7.68-7.71 (m, 1 H), 7.39-7.45 (m, 2 H), 7.32-7.35 (q, 1 H), 6.82-6.90 (bs, 1 H), 6.72 (d, 1H), 5.19-5.23 (q, 1 H), 4.67 (d, 1 H), 4.03-4.09 (m, 2 H), 3.97-4.02 (m, 1 H), 3.65-3.71 (m, 2 H), 3.05-3.10 (m, 2 H), 2.51-2.53 (m, 1 H), 2.01-2.09 (m, 2 H), 1.85-1.91 (m, 1 H), 1.76-1.82 (m, 2 H), 1.31-1.40 (m, 2 H) *m/z* 489.6 (M+1)
26		1H NMR (DMSO-d6) 8.13 (s, 1 H), 7.92 (d, 1 H), 7.74-7.98 (bs, 1 H), 7.68-7.66 (bs, 1 H), 7.36-7.40 (m, 1 H), 7.14-7.20 (m, 2 H), 7.00-7.06 (m, 1 H), 6.80-6.92 (bs, 1 H), 6.70 (d, 1H), 5.16-5.20 (q, 1 H), 4.47-4.56 (m, 2 H), 3.98-4.03(m, 1 H), 3.65-3.71 (m, 1 H), 3.03-3.20 (m, 2 H), 2.70-2.95 (m,4 H), 2.45-2.50 (m, 1 H), 2.00-2.08 (m, 2 H), 1.85-1.90 (m, 1 H), 1.71-1.83 (m, 4 H) *m/z* 473.6 (M+1)
27		1H NMR (DMSO-d6) 8.06 (s, 1 H), 7.88 (d, 1 H), 7.42-7.60 (m, 2 H), 7.34-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.00-7.05 (m, 1 H), 6.75-6.85 (bs, 1 H), 6.73 (d, 1H), 5.14-5.19 (q, 1 H), 3.96-4.01 (m, 1 H), 3.64-3.70 (q, 1 H), 3.48-3.58 (bs, 4 H), 3.15-3.24 (bs, 2 H), 3.04 (s, 3H), 2.82 (s, 3 H), 2.50-2.60 (bs, 4 H), 2.45-2.50 (m, 1 H), 2.01-2.06 (m, 2 H), 1.84-1.89 (m, 1 H) *m/z* 529.6 (M+1)
28		1H NMR (DMSO-d6) 8.05 (s, 1 H), 7.88 (d, 1 H), 7.42-7.60 (m, 2 H), 7.35-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.00-7.05 (m, 1 H), 6.76-6.86 (bs, 1 H), 6.71 (d, 1H), 5.15-5.17 (q, 1 H), 3.96-4.01 (m, 1 H), 3.64-3.70 (q, 1 H), 3.46-3.54 (bs, 4 H), 2.64-2.71 (m, 1

		H), 2.50-2.56 (bs, 4 H), 2.45-2.50 (m, 1 H), 2.00-2.06 (m, 2 H), 1.84-1.90 (m, 1 H), 1.00 (d, 6 H) *m/z* 486.6 (M+1)
29		1H NMR (DMSO-d6) 8.04 (s, 1 H), 7.88 (d, 1 H), 7.34-7.50 (m, 3 H), 7.12-7.37 (m, 2 H), 7.00-7.16 (m, 1 H), 6.76-6.84 (bs, 1H), 6.72 (d, 1H), 5.15-5.18 (q, 1 H), 4.45 (d, 1 H), 4.01 (s, 1 H), 3.96-4.01 (m, 1 H), 3.64-3.68 (m, 1 H), 2.65-2.71 (m, 2 H), 2.44-2.48 (m, 1 H), 2.00-2.06 (m, 2 H), 1.84-1.89 (m, 1 H), 1.74-1.79 (m, 2 H), 1.38-1.45 (m, 1 H), 1.18-1.28 (m, 2 H), 1.04 (s, 6 H), 0.82-.088 (m, 1H) *m/z* 501.6 (M+1)
30		1H NMR (DMSO-d6) 8.04 (s, 1 H), 7.87 (d, 1 H), 7.40-7.52 (m, 2 H), 7.34-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.00-7.05 (m, 1 H), 6.77-6.85 (bs, 1H), 6.74 (d, 1H), 5.14-5.18 (q, 1 H), 4.36 (d, 2 H), 3.96-4.01 (m, 1 H), 3.63-3.69 (q, 1 H), 3.55 (t, 4 H), 2.80 (t, 2 H), 2.42-2.50 (m, 5 H), 2.34-2.40 (m, 1 H), 2.00-2.05 (m, 2 H), 1.82-1.89 (m, 3 H), 1.33-1.41 (m, 2 H) *m/z* 528.6 (M+1)
31		1H NMR (DMSO-d6) 8.06 (s, 1 H), 7.88 (d, 1 H), 7.41-7.60 (m, 2 H), 7.34-7.40 (m, 1 H), 7.12-7.18 (m, 2 H), 7.00-7.15 (m, 1 H), 6.77-6.85 (bs, 1H), 6.74 (d, 1H), 5.15-5.18 (q, 1 H), 3.96-4.01 (m, 1 H), 3.64-3.70 (q, 1 H), 3.54 (t, 4 H), 2.72 (t, 2 H), 2.62 (t, 2 H), 2.51-2.55 (m, 4 H), 2.45-2.50 (m, 1 H), 2.00-2.06 (m, 2 H), 1.84-1.90 (m, 1 H) *m/z* 497.6 (M+1)

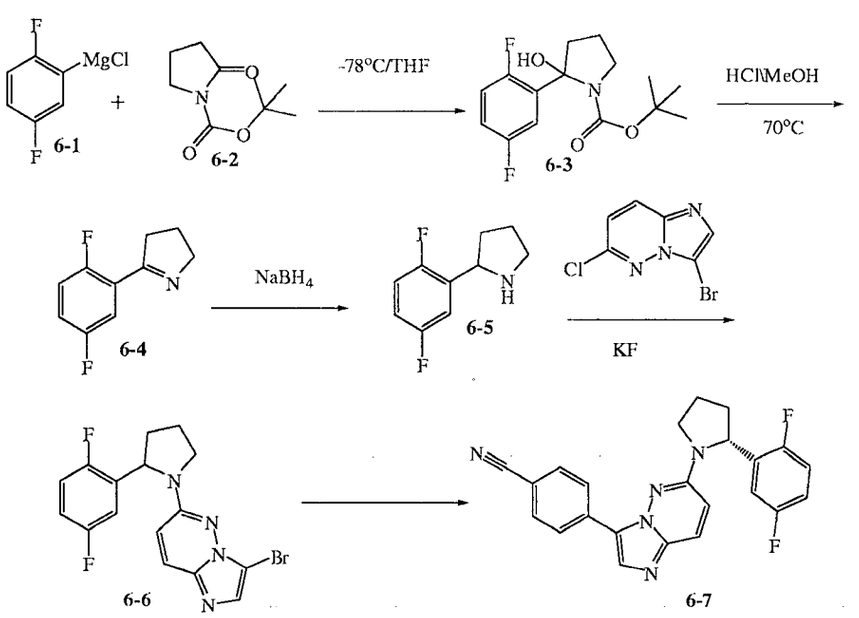
32		1H NMR (DMSO-d6) 8.07 (s, 1 H), 7.88 (d, 1 H), 7.50-7.58 (bs, 1 H), 7.42-7.48 (bs, 1 H), 7.35-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.01-7.05 (m, 1 H), 6.78-6.85 (bs, 1 H), 6.73 (d, 1H), 5.15-5.18 (q, 1 H), 3.96-4.01 (m, 1 H), 3.87-3.94 (m, 1 H), 3.64-3.70 (m, 1 H), 3.54-360 (bs, 4 H), 2.91-2.96 (bs, 2 H), 2.50-2.60 (bs, 4 H), 2.45-2.50 (m, 1 H), 2.00-2.06 (m, 2 H), 1.84-1.90 (m, 1 H), 1.08 (d, 6 H) *m/z* 543.7 (M+1)
33		1H NMR (DMSO-d6) 8.04 (s, 1 H), 7.87 (d, 1 H), 7.40-7.50 (m, 2 H), 7.35-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.01-7.05 (m, 1 H), 6.76-6.85 (bs, 1H), 6.72 (d, 1H), 5.14-5.17 (q, 1 H), 4.46 (t, 1 H), 4.37 (d, 2 H), 3.96-4.01 (m, 1 H), 3.64-3.69 (q, 1 H), 3.27 (t, 2 H), 2.74-2.81 (m, 2 H), 2.45-2.50 (m, 1 H), 2.00-2.06 (m, 2 H), 1.84-1.89 (m, 1 H), 1.58-1.64 (m, 1 H), 1.08-1.17 (m, 2 H) *m/z* 473.6 (M+1)
34		1H NMR (DMSO-d6) 8.05 (s, 1 H), 7.88 (d, 1 H), 7.40-7.50 (m, 2 H), 7.34-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.00-7.05 (m, 1 H), 6.76-6.85 (bs, 1H), 6.69 (t, 1 H), 5.15-5.18 (q, 1 H), 4.54-4.57 (m, 1 H), 4.34 (d, 1 H), 4.22 (d, 1 H), 3.96-4.02 (m, 1 H), 3.64-3.70 (q, 1 H), 3.28-3.37 (m, 2 H), 2.81-2.88 (m, 1 H), 2.59 (t, 1 H), 2.45-2.50 (m, 1 H), 2.00-2.08 (m, 2 H), 1.84-1.90 (m, 1 H), 1.72-1.77 (m, 1 H), 1.66-1.72 (m, 1 H), 1.58-1.65 (m, 1 H), 1.40-1.59 (m, 1 H), 1.14-1.22 (m, 1 H) *m/z* 473.6 (M+1)
35		1H NMR (DMSO-d6) 8.07 (s, 1 H), 7.88 (d, 1 H), 7.41-7.60 (m, 2 H), 7.34-7.40 (m, 1 H), 7.12-7.18 (m, 2 H), 7.00-7.15 (m, 1 H), 6.78-6.85 (bs, 1H), 6.77 (d, 1H),

		5.15-5.18 (q, 1 H), 3.96-4.01 (m, 1 H), 3.83-3.89 (m, 2 H), 3.64-3.70 (q, 1 H), 3.09-3.14 (m, 1 H), 2.45-2.50 (m, 1 H), 2.00-2.06 (m, 2 H), 1.94-1.97 (m, 2 H), 1.84-1.89 (m, 1 H), 1.71-1.77 (m, 2 H) *m/z* 468.5 (M+1)
36		1H NMR (DMSO-d6) 8.05(s, 1 H), 7.88 (d, 1 H), 7.42-7.60 (m, 2 H), 7.35-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.00-7.05 (m, 1 H), 6.75-6.85 (bs, 1H), 6.72 (d, 1H), 5.14-5.18 (q, 1 H), 4.43 (t, 1 H), 3.96-4.01 (m, 1 H), 3.63-3.70 (q, 1 H), 3.47-3.57 (m, 6 H), 2.50-2.55 (m, 4 H), 2.40-2.50 (m, 3 H), 2.00-2.06 (m, 2 H), 1.84-1.89 (m, 1 H) *m/z* 488.6 (M+1)
37		1H NMR (DMSO-d6) 8.07 (s, 1 H), 7.88 (d, 1 H), 7.46-7.68 (m, 2 H), 7.36-7.40 (q, 1 H), 7.12-7.18 (m, 2 H), 7.00-7.06 (m, 1 H), 6.78-6.88 (bs, 1 H), 6.73 (d, 1 H), 5.15-5.18 (q, 1 H), 3.96-4.01 (m, 1 H), 3.70-3.73 (m, 4 H), 3.64-3.69 (q, 1 H), 3.46-3.51 (m, 4 H), 2.45-2.50 (m, 1 H), 2.01-2.06 (m, 2 H), 1.84-1.89 (m, 1 H) *m/z* 445.5 (M+1)
38		*m/z* 488.3 (M+1)
39		*m/z* 500.3 (M+1)

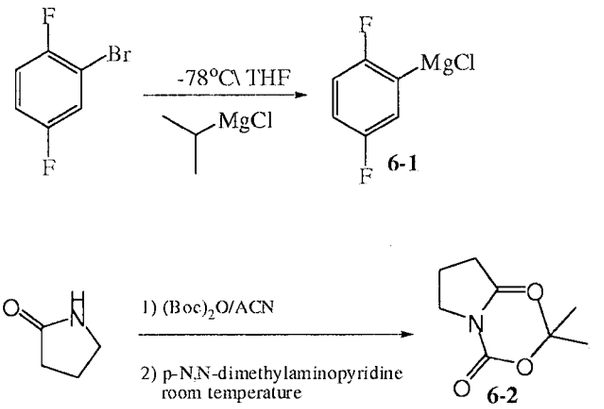
40		*m/z* 486.3 (M+1)
41		1H NMR (DMSO-d6): d 8.06 (s, 1 H), 7.75 (s, 1 H), 7.51 (d, 1 H), 7.32-7.40 (m, 2 H), 7.22 (d, 1 H), 7.14 (d, 2 H), 6.99-7.05 (m, 1 H), 6.45-6.50 (m, 1 H), 6.35 9d, 1 H), 4.14-4.21 (m, 1 H), 3.30-3.39 (m, 2 H), 2.82 (d, 3 H), 2.17-2.26 (m, 1 H), 2.00-2.10 (m, 1 H), 1.56-1.83 (m, 3 H), 1.35-1.50 (m, 1 H) *m/z* 403.2 (M+1)
42		1H NMR (DMSO-d6): d 8.02 (s, 1 H), 7.90 (d, 1 H), 7.46 (d, 1 H), 7.30-7.40 (m, 2 H), 7.21 (d, 1 H), 7.13 (d, 2 H), 6.98-7.06 (m, 1 H), 6.30-6.36 (m, 2 H), 4.12-4.20 (m, 1 H), 4.02-4.10 (m, 1 H), 3.30-3.38 (m, 2 H), 2.18-2.26 (m, 1 H), 2.00-2.10 (m, 1 H), 1.56-1.84 (m, 3 H), 1.36-1.48 (m, 1 H), 1.17 (d, 6 H) *m/z* 431.2 (M+1)
43		1H NMR (DMSO-d6): d 10.63 (s, 1 H), 8.06 (s, 1 H), 7.97 (s, 1 H), 7.94 (d, 1 H), 7.72 (t, 1 H), 7.33-7.40 (m, 1 H), 7.25 (d, 1 H), 7.12-7.18 (m, 2 H), 6.99-7.05 (m, 1 H), 6.80 (d, 1 H), 4.15-4.22 (m, 1 H), 3.42 (s, 3 H), 3.35-3.42 (m, 2 H), 2.17-2.26 (m, 1 H), 2.01-2.14 (m, 1 H), 1.57-1.85 (m, 3 H), 1.36-1.49 (m, 1 H) *m/z* 467.2 (M+1)
44		*m/z* 417.3 (M+1)

45		*m/z* 473.3 (M+1)
46		*m/z* 459.2 (M+1)
47		*m/z* 431.1 (M+1)
48		*m/z* 461.5 (M+1)

Scheme 6A



Scheme 6B



Example 6

(R)-4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile

[000390] (R)-4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile (6-7) was synthesized from (2,5-difluorophenyl)magnesium chloride (6-1) and tert-butyl 2-oxopyrrolidine-1-carboxylate (6-2) in five steps as shown in scheme 6A. (2,5-difluorophenyl)magnesium chloride (6-1) and tert-butyl 2-oxopyrrolidine-1-carboxylate (6-2) were synthesized as shown in reaction scheme 6B.

[000391] To synthesize (2,5-difluorophenyl)magnesium chloride (6-1), a solution of 2-bromo-1,4-difluorobenzene (10g, 52 mmol) in 30 mL of anhydrous THF was cooled to -78°C under argon and then 27 mL of isopropylmagnesium chloride in THF (2.0 M, 54 mmol) was added drop-wise. The reation mixture was warmed to between -20°C and -30°C for 30 minutes, and then cooled to -78°C until used in the synthesis of tert-butyl 2-(2,5-difluorophenyl)-2-hydroxypyrrolidine-1-carboxylate (6-3) without further purification.

[000392] To synthesize tert-butyl 2-oxopyrrolidine-1-carboxylate (7-2), p-N,N-dimethylaminopyridine (0.7 g, 5.9 mmol) was added at room temperature to a solution of 2-pyrrolidone (5g, 59 mmol) and di-tert-butyl dicarbonate (26 g, 118mmol) in 100 mL of acetonitrile. The reaction mixure was stirred for 3 hours and the acetonitrile was removed using a rotary evaporator resulting in a light orange residue. The residue was reconstituted in ethyl acetate (300 mL) and the organic layer washed with brine (3 x 150 mL). The organic layer was dried with sodium sulfate and the ethyl acetate was removed using a rotary evaporator resulting in tert-butyl 2-oxopyrrolidine-1-carboxylate (6-2) as a light orange residue.

[000393] In step 6A-1, (2,5-difluorophenyl)magnesium chloride (6-1) was added drop-wise to a solution of tert-butyl 2-oxopyrrolidine-1-carboxylate (6-2) (9.6 g, 52 mmol) in THF under argon at -78°C. A maximum of 5 mL aliquots was used to minimize the temperature increase of the magnesium chloride reagent. The resulting solution was then stirred at -78°C for one hour. The solution was then warmed to room temperature and quenched with concentrated HCl (4 mL). The solvent was then removed using a rotary evaporator resulting in a light yellow residue. The residue was then reconstituted in ethyl acetate and

extracted with brine (3x150 mL). The organic layer was then dried using sodium sulfate. The ethyl acetate was removed yielding tert-butyl 2-(2,5-difluorophenyl)-2-hydroxypyrrolidine-1-carboxylate (6-3) as a light yellow oil. m/z = 300 [M+1] The product was used without further purification.

[000394] In step 6A-2, concentrated hydrochloric acid (23 mL, 260 mmol) was added to a solution of tert-butyl 2-(2,5-difluorophenyl)-2-hydroxypyrrolidine-1-carboxylate (6-3) (15.6 g, 52 mmol) in methanol. The reaction mixture was heated to 70°C while stirring and was then stirred at 70°C for 6 hours. The reaction mixture was cooled to room temperature and neutralized with a 7.5 M solution of sodium hydroxide (35 mL, 263 mmol). The methanol was removed and the resulting slurry was reconstituted with ethyl acetate (250 mL). The organic layer was washed with brine (3x150 mL), and then dried with sodium sulfate. The ethyl acetate was then removed to yield 5-(2,5-difluorophenyl)-3,4-dihydro-2H-pyrrole (6-4) as a light yellow oil. m/z = 182.2 [M+1].

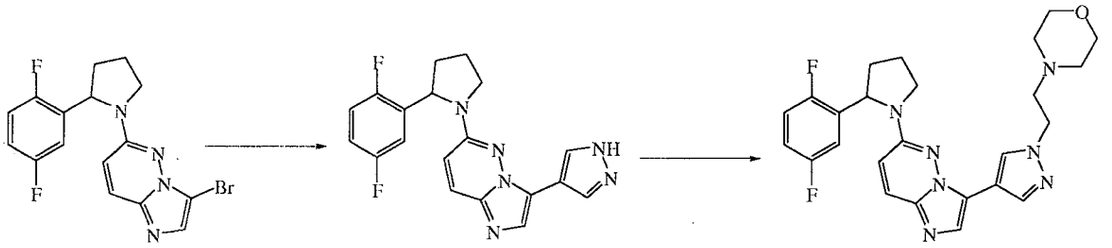
[000395] In step 6A-3, sodium borohydride (2.1 g, 55.2 mmol) was added at room temperature to a solution of 5-(2,5-difluorophenyl)-3,4-dihydro-2H-pyrrole (6-4) (5.0 g, 28 mmol) in anhydrous ethanol (150 mL). The reaction mixure was stirred over-night at room temperature. The ethanol was removed using a rotary evaporator and the resulting orange solid was reconstituted with ethyl acetate. The organic layer was washed with brine (3x150 mL), dried with sodium sulfate and the. ethyl acetate was removed to yield 2-(2,5-difluorophenyl)pyrrolidine (6-5) as a light yellow oil. m/z = 184.2 [M+1].

[000396] In step 6A-4, 2-(2,5-difluorophenyl)pyrrolidine (6-5) (1.7 g, 9.3 mmol) was added to a solution of 3-bromo-6-chloroimidazo[1,2-b]pyridazine (11-1) (1.1 g, 230.92) and potassium fluoride (2.7 g, 46 mmol) in DMSO (10 mL). The resulting solution was heated to130°C and stirred over-night. The resulting dark orange slurry was cooled to room temperature, poured into 50mL of DI water and extracted with ethyl acetate (3x150 mL). The ethyl acetate was dried with sodium sulfate and then removed to yield an orange solid. This solid was reconstituted with minimal amounts of dichloromethane (DCM) and purified using a silica gel column (40g, ISCO) and a 0-5% gradient of methanol:DCM over a 20 minute period followed by 5% methanol for an additional 10 minutes. The solvent was removed from the desired fractions to yield 3-bromo-6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine (6-6) as a light yellow solid. m/z = 379.2 [M+1].

[000397] In step 6A-5, palladium tetrakis (25 mg, 0.02 mmol) was added to a solution of 3-bromo-6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine (6-6) (77 mg, 0.23 mmol), sodium carbonate (85 mg, 0.81 mmol), and 4-cyanophenylboronic acid (60mg, 0.41mmol) in 2mL of dioxane and 0.5 mL of water contained in a microwave reaction tube. The resulting solution was heated in a microwave for 25 minutes at 150°C and the yellow slurry was cooled to room temperature and filtered through a 0.2μm nylon frit. The solvent was removed from the mother liquor and the remaining residue was reconstituted in methanol and further purified by preparative LC/MS. The desired fractions were dried to yield the desired product as a racemic mixture, which was then purified by chiral LC to yield (R)-4-(6-(2-(2,5-

difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile (6-7) as a chiral pure white solid along with (S)-4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile as a chiral pure white solid.

Scheme 7



Example 7

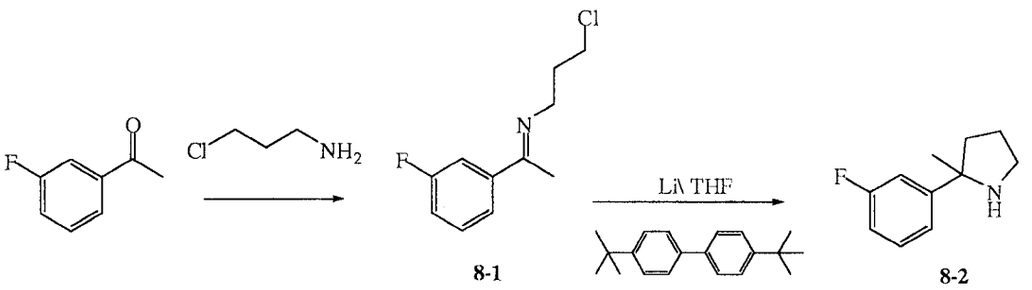
4-(2-(4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1H-pyrazol-1-yl)ethyl)morpholine

[000398] 4-(2-(4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1H-pyrazol-1-yl)ethyl)morpholine (7-2) was synthesized in two steps as shown in scheme 7.

[000399] In step 7-1, $[Pd(dppf)_2]Cl_2$ (54 mg, 0.07mmol) in 2.5 mL of 1,4-dioxane and 0.5 mL of water was added to a solution of 3-bromo-6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine (6-6) (0.25g, 0.7mmol), sodium carbonate (0.25g, 2.5 mmol), and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.27g, 1.4 mmol) contained in a microwave reaction tube. The reaction mixture was heated in the microwave for twenty minutes at 150°C, and the yellow slurry was then cooled to room temperature and filtered through a 0.2μM nylon frit. The solvent was removed from the mother liquor and the remaining residue was reconstituted in dichloromethane (DCM). This solution was loaded onto a 12g silica gel column and eluted using a 0-5% methanol in DCM gradient over 30 minutes. The solvent was removed from the desired fractions to yield 6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine(7-1) as an off-white solid. m/z = 367.4 [M+1].

[000400] In step 7-2, 4-(2-chloroethyl)morpholine hydrochloride (40mg, 0.2 mmol) was added to a solution of 6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (7-1) (35mg, 0.1mmol) and cesium carbonate (100mg, 0.35mmol) in DMF (5mL). The reaction mixture was stirred at room temperature over-night and the DMF was then removed using a rotary evaporator. The resulting residue was reconstituted in ethyl acetate (30 mL) and the organic layer extracted with brine and then dried using sodium sulfate. The ethyl acetate was removed and the product was further purify by preparative LC/MS to yield 4-(2-(4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1H-pyrazol-1-yl)ethyl)morpholine (7-2) as a white solid. m/z = 480.2 [M+1].

Scheme 8



Example 8

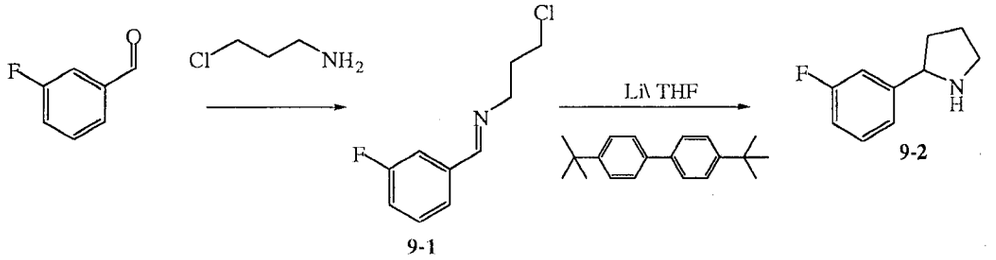
2-(3-fluorophenyl)-2-methylpyrrolidine

[000401] 2-(3-fluorophenyl)-2-methylpyrrolidine (8-2) was synthesized in two steps as shown in scheme 8.

[000402] In step 8-1, 3-chloropropan-1-amine hydrochloride (4.1g, 32 mmol) was added to a suspension of 1-(3-fluorophenyl)ethanone (4.4g, 32 mmol) and sodium carbonate (3.7 g, 35 mmol) in water (15 mL). The reaction mixture was stirred overnight and the resulting solution was then extracted with ethyl acetate (3x150 mL). The organic layer was dried with sodium sulfate, and the ethyl acetate removed to yield 3-chloro-N-(1-(3-fluorophenyl)ethylidene)propan-1-amine (8-1) as a light yellow oil. m/z = 214.0 [M+1].

[000403] In step 8-2, 3-chloro-N-(1-(3-fluorophenyl)ethylidene)propan-1-amine (8-1) (4.7 g, 22 mmol) was added at -78°C to a solution of lithium granules (0.8g, 110 mmol) and 4,4'-di-tert-butylbiphenyl (0.6g, 2.2 mmol) in THF (40 mL) cooled to -78°C. The resulting solution was stirred at -78°C for 2 hours then quenched with water and the temperature was allowed to increase to 20°C. Solids were then removed by filtration, the mother liquor was reduced using a rotary evaporator and the resulting residue was reconstituted in ethyl acetate. The organic was washed with 1N HCl (3x25 mL) and the aqueous layer extracted with ethyl acetate. The aqueous layer was neutralized with 1N NaOH solution and extracted with ethyl acetate (3x100 mL). The organic layer was dried with sodium sulfate and the solvent removed to yield 2-(3-fluorophenyl)-2-methylpyrrolidine (8-2) as a light yellow oil. m/z = 180.3 [M+1].

Scheme 9



Example 9

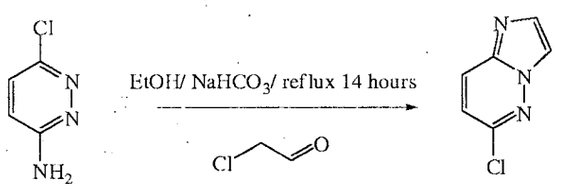
2-(3-fluorophenyl)pyrrolidine

[000404] 2-(3-fluorophenyl)pyrrolidine (9-2) was synthesized in two steps as shown in scheme 9.

[000405] In step 9-1, 3-chloropropan-1-amine hydrochloride (43g, 331 mmol) was added to a suspension of 3-fluorobenzaldehyde (41g, 331 mmol) and sodium carbonate (39 g, 364 mmol) in water (100 mL) and the resulting slurry was stirred over-night. The resulting solution was extracted with ethyl acetate (3x150 mL)and the organic layer dried with sodium sulfate. The ethyl acetate was removed to yield 3-chloro-N-(3-fluorobenzylidene)propan-1-amine (9-1) as a light yellow oil m/z = 200.0 [M+1].

[000406] In step 9-2, 3-chloro-N-(3-fluorobenzylidene)propan-1-amine (9-1) (53 g, 266 mmol) was added at -78°C to a solution of lithium granules (5.5g, 800 mmol) and 4,4'-di-tert-butylbiphenyl (5.7g, 21 mmol) in THF (50 mL) cooled to -78°C. The resulting solution was stirred at -78°C for 2 hours then quenched with water and the temperature was allowed to rise up to 20°C. The solids were removed by filtration and the mother liquor was reduced using a rotary evaporator. The resulting residue was reconstituted in ethyl acetate, the organic washed with 1N HCl (3x25 mL) and the aqueous layer was extracted with ethyl acetate. The aqueous layer was then neutralized with 1N NaOH solution and the aqueous layer was extracted with ethyl acetate (3x100 mL). The organic layer was dried with sodium sulfate and the solvent was removed to yield 2-(3-fluorophenyl)pyrrolidine (9-2) as a light yellow oil. m/z = 165.2 [M+1].

Scheme 10



10-1

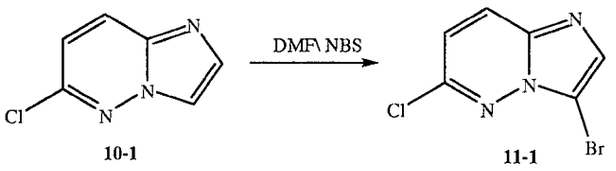
Example 10

Chloro-imidazo[1,2-b]pyridazine.

[000407] Chloro-imidazo[1,2-b]pyridazine (10-1) was synthesized as shown in scheme 10, wherein chloracetaldehyde (55% in water, 126 ml, 880 mmol) was added to a solution of 6-chloro-pyridazin-3-ylamine (25.43 g, 196 mmol) and $NaHCO_3$ (28 g, 334 mmol) in EtOH (600 ml) and then the reaction mixture was heated to reflux while stirring for 14 hours. The resulting dark brown reaction mixture was then concentrated under vacuum and the resulting residue reconstituted with dichloromethane (DCM). This solution was filtered through a celite pad and the the solid washed with DCM and the solvent was then removed to yield a dark brown oil. 2M HCl (290 ml) and water (300 ml) was added to the residue and the

resulting slurry was stirred at room temperature for 15 minutes. The solution was filtered through a celite pad and the filter cake was washed with water. The filtrate was extracted with diethyl ether (3 x 200 ml). The aqueous layer was cooled to 0°C (ice bath) and neutralized using NaOH (24 g). The resulting slurry was extracted with diethyl ether (6 x 300 ml), dried using sodium sulfate and the diethyl ether was removed using a rotary evaporator to yield chloro-imidazo[1,2-b]pyridazine (10-1) as a light orange solid. MS: 155.1 $[M+1]^+$.

Scheme 11



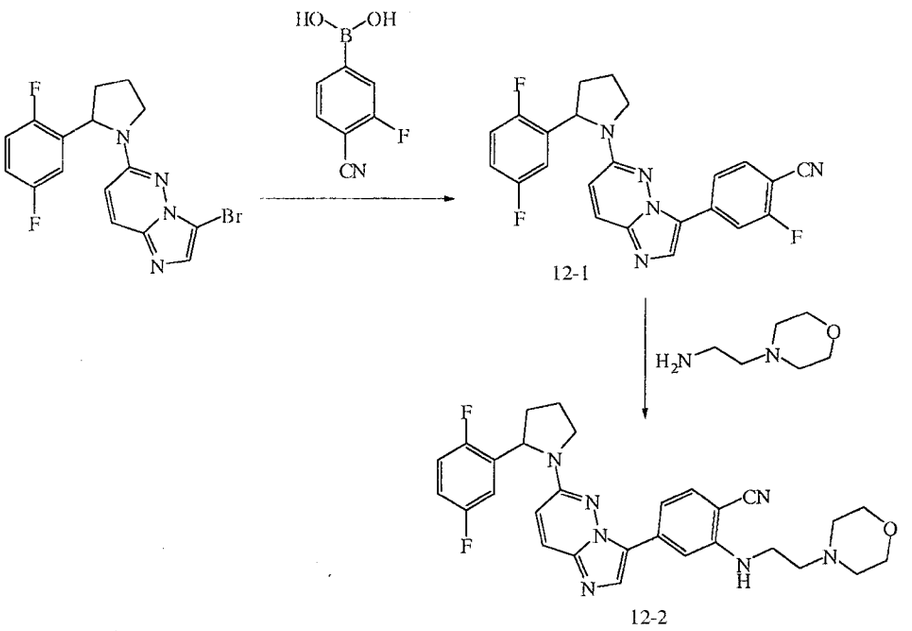
10-1 11-1

Example 11

3-bromo-6-chloroimidazo[1,2-b]pyridazine

[000408] 3-bromo-6-chloroimidazo[1,2-b]pyridazine (11-1) was synthesized as shown in scheme 11, wherein N-bromosuccinamide (19.2 g, 108 mmol) was added to a solution of chloro-imidazo[1,2-b]pyridazine (10-1) (15 g, 98 mmol) in DMF cooled to 0°C. The resulting solution was stirred at 0°C for 1 hour and the reaction mixture was then poured into 1.4L of stirring water at room temperature. The resulting yellow heterogeneous solution was then stirred at room temperature for one hour and the solids were then filtered and washed with hexanes. The solid was dried under vacuum over-night to yield 3-bromo-6-chloroimidazo[1,2-b]pyridazine (11-1) as a yellow solid.

Scheme 12



Example 12
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-morpholinoethylamino)benzonitrile

[000409] 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-morpholinoethylamino)benzonitrile (12-2) was synthesized in two steps as shown in scheme 12.

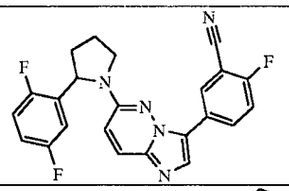
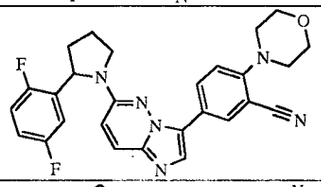
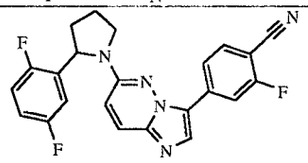
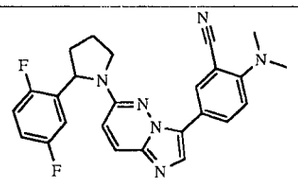
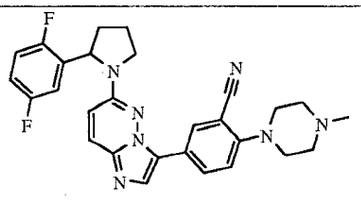
[000410] In step 12-1, $[Pd(Dppf)_2]Cl_2$ (90 mg, 0.11 mmol), sodium carbonate (0.41 g, 3.9 mmol), and 4-cyano-3-fluorophenylboronic acid (0.36 g, 2.2 mmol) were added to a solution of 3-bromo-6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine (6-6) (0.42 g, 1.1 mmol) in 3 mL of dioxane and 1 mL of DI water. The reaction mixture was heated in a microwave for twenty minutes at 150°C, and the slurry was then cooled to room temperature and filtered through a 0.2μM nylon frit. The solvent was removed from the mother liquor and the remaining residue was reconstituted in dichloromethane (DCM). This solution was loaded onto a 12g silica gel column and eluted using a 0-10% methanol in DCM gradient over 30 minutes. The solvent was removed from the desired fractions to yield 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-fluorobenzonitrile. m/z = 420.2 [M+1].

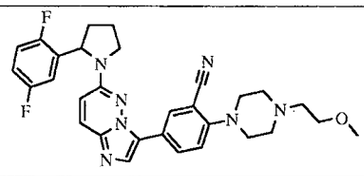
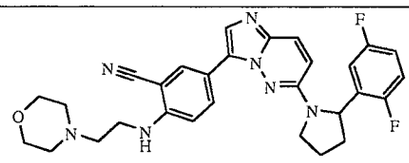
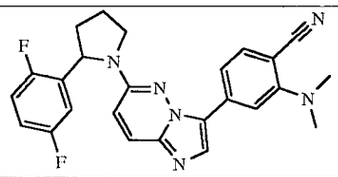
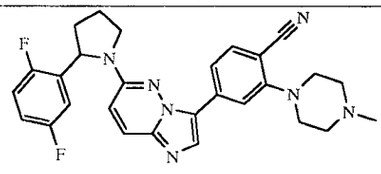
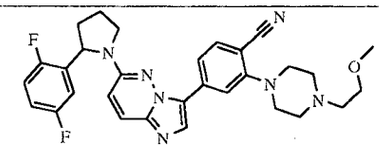
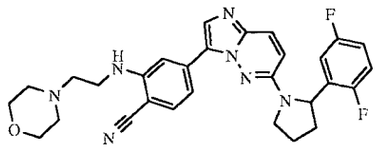
[000411] In step 12-2, 2-morpholinoethanamine (30 mg, 0.30 mmol) was added to 4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-fluorobenzonitrile (40 mg, 0.13 mmol) in 1mL of DMF. The resulting mixture was heated to110°C and stirred for 12 hours at 110°C. The product was then purified using mass triggered preparatory LC/MS giving 1-(6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol (13-2). ^1H NMR (400 MHz, D_6 Dimethylsulfoxide) 8.050 (s, 1H) 7.854 (d, 0.025, 1H) 7.434 (br s, 1H) 7.327 (dt, J = 0.023, 0.011, 1H) 7.262 (m, 1H) 7.173 (m, 1H) 7.070 (m, 1H) 6.937 (m, 1H) 6.747 (br s, 1H) 5.770 (t, J = 0.012,

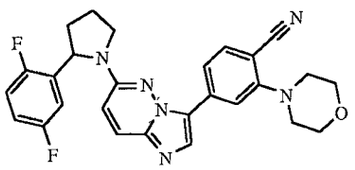
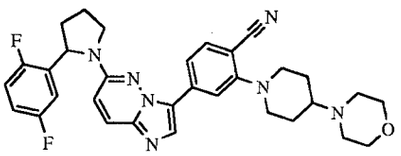
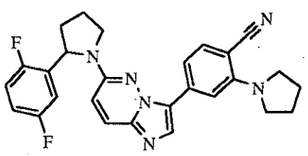
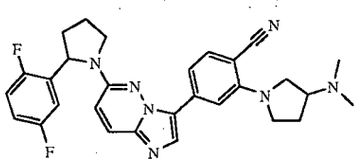
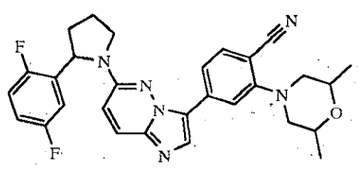
1H) 5.244 (d, J = 0.019, 1H) 3.949 (dt, J = 0.017, 0.006, 1H) 3.575 (q, J = 0.023, 1H) 3.522 (t, J = 0.011, 4H) 3.268 (m, 4H) 2.536 (t, J = 0.016, 2H) 1.985 (m, 3H) LCMS *m/z* 530.2 [M+1]

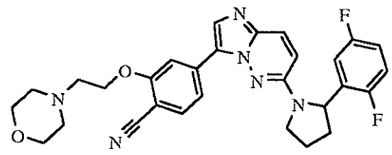
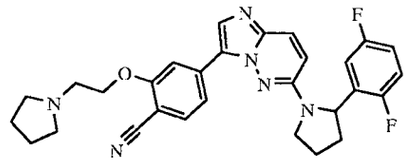
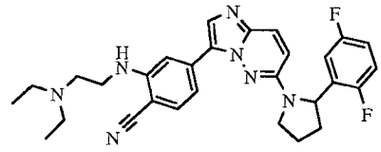
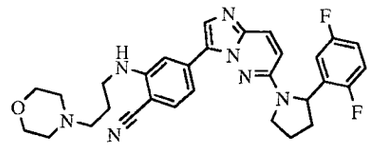
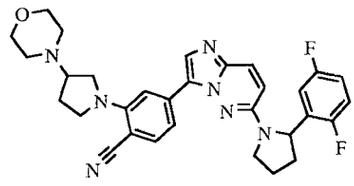
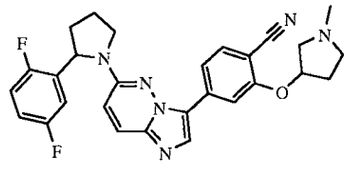
[000412] By repeating the procedures described in the above examples, using appropriate starting materials, the following compounds of Formula (I), as identified in Table 5, were obtained.

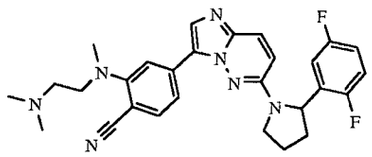
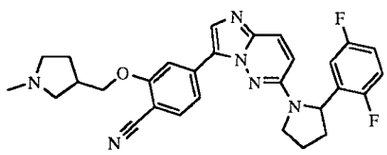
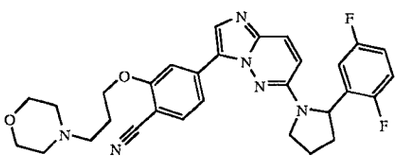
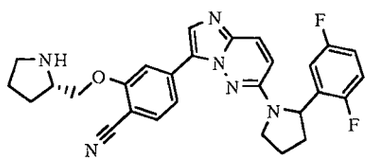
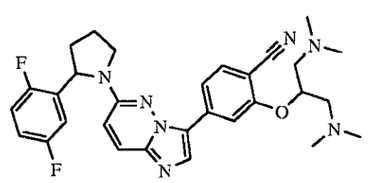
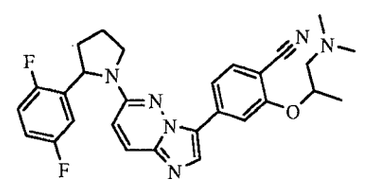
Table 5

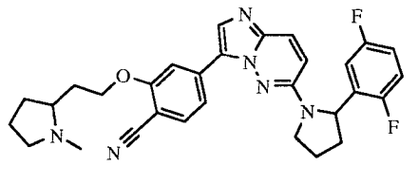
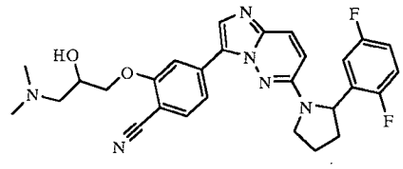
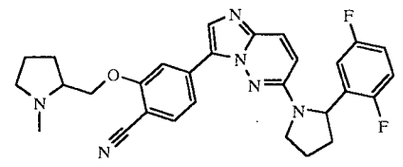
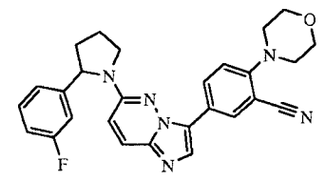
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
1		420.4 (M+H)
2		487.5 (M+H)
3		487.5 (M+H)
4		8.247 (s, 1H) 8.192 (br s, 1H) 8.071 (d, J = 0.024, 1H) 7.926 (br s, 1H) 7.341 (dt, J= 0.024, 0.011, 1H) 7.139 (m, 2H) 7.037 (m, 1H) 6.929 (m, 1H) 5.332 (d, J = 0.018, 1H) 4.033 (m, 1H) 3.652 (q, J = 0.023, 2H) 3.090 (s, 6H) 2.122 (m, 3H) 445.5 (M+H)
5		8.212 (br s, 1H) 8.019 (br s, 1H) 7.927 (s, 1H) 7.849 (d, J = 0.024, 1H) 7.274 (dt, J= 0.024, 0.012, 1H)7.046 (m, 1H) 6.950 (m, 2H) 6.782 (m, 1H) 5.250 (d, J = 0.019, 1H) 3.933 (dt, J = 0.024, 0.006, 1H) 3.553 (q, 0.022, 1H) 3.132 (t, J= 0.012, 3H) 2.473 (m, 6H) 2.197 (s, 3H) 1.986 (m, 3H)

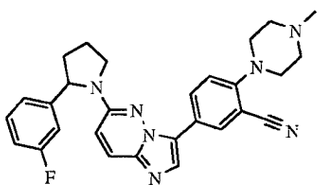
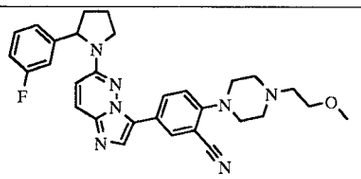
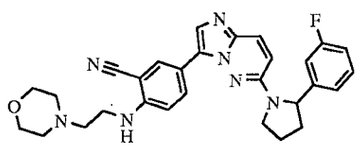
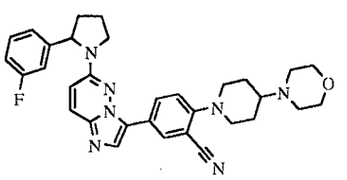
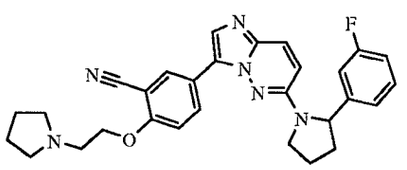
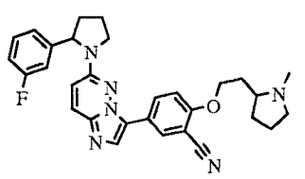
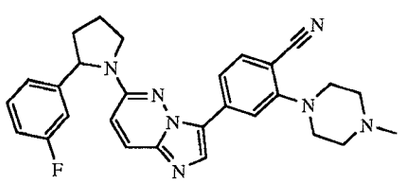
		500.6 (M+H)
6		544.6 (M+H)
7		530.6 (M+H)
8		445.5 (M+H)
9		9.935 (br s, 1H) 8.364 (s, 1H) 8.019 (d, J = 0.024, 1H) 7.626 (m, 2H) 7.430 (dt, J = 0.024, 0.011, 1H) 7.153 (m, 1H) 7.033 (m, 2H) 5.325 (d, J = 0.019, 1H) 4.035 (dt, J = 0.019, 0.006, 1H) 3.727 (d, J = 0.028, 2H) 3.603 (m, 3H) 3.241 (m, 4H) 2.926 (s, 3H) 2.090 (m, 4H) 500.6 (M+H)
10		9.840 (br s, 1H) 8.335 (s, 1H) 8.007 (d, J = 0.025, 1H) 7.622 (m, 2H) 7.429 (m, 1H) 7.153 (m, 1H) 7.033 (m, 2H)5.324 (d, J = 0.019, 1H) 4.035 (dt, J =0.019, 0.007, 1H) 3.724 (m, 9H) 3.357 (s, 3H) 3.305 (m, 4H) 2.122 (m, 4H) 544.6 (M+H)
11		8.050 (s, 1H) 7.854 (d, 0.025, 1H) 7.434 (br s, 1H) 7.327 (dt, J = 0.023, 0.011, 1H) 7.262 (m, 1H) 7.173 (m, 1H) 7.070 (m, 1H) 6.937 (m, 1H) 6.747 (br s, 1H) 5.770 (t, J = 0.012, 1H) 5.244 (d, J = 0.019, 1H) 3.949 (dt, J =

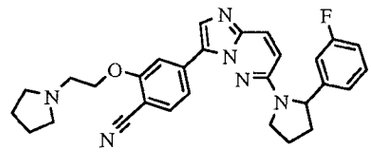
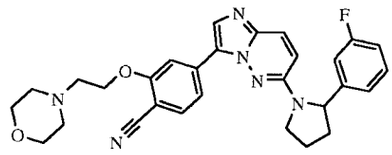
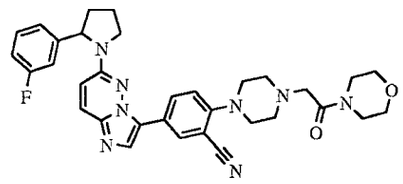
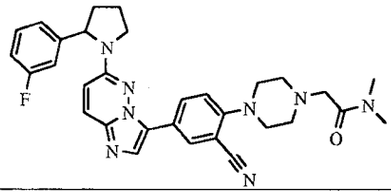
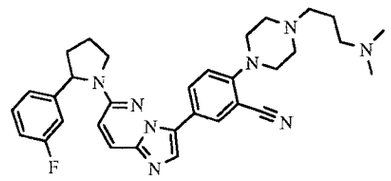
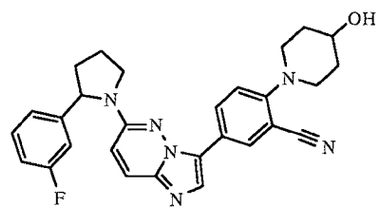
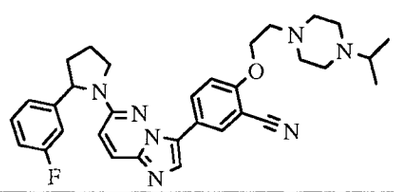
		0.017, 0.006, 1H) 3.575 (q, J = 0.023, 1H) 3.522 (t, J = 0.011, 4H) 3.268 (m, 4H) 2.536 (t, J = 0.016, 2H) 1.985 (m, 3H) 530.6 (M+H)
12		487.5 (M+H)
13		9.908 (br s, 1H) 8.362 (s, 1H) 8.046 (d, J = 0.025, 1H) 7.600 (br s, 2H) 7.437 (dt, J =0.024, 0.011, 1H) 7.155 (m, 1H) 7.032 (m, 2H) 5.330 (d, J = 0.019, 1H) 4.035 (d, J = 0.024, 3H) 3.698 (m, 5H) 3.543 (d, J = 0.030, 2H) 3.409 (m, 2H) 3.182 (m, 2H) 2.898 (t, J = 0.030, 2H) 2.277(d, J = 0.026, 2H) 1.950 (m, 5H) 570.6 (M+H)
14		8.230 (s, 1H) 7.910 (d, J = 0.025, 1H) 7.239 (m, 2H) 7.008 (m, 3H) 6.867 (m, 2H) 5.178 (d, J = 0.020, 1H) 3.883 (t, J = 0.019, 2H) 3.441 (m, 5H) 1.829 (m, 7H) 471.5 (M+H)
15		9.934 (br s, 1H) 8.264 (s, 1H) 7.994 (d, J = 0.025, 1H) 7.419 (m, 3H) 7.154 (m, 1H) 7.024 (m, 2H) 5.310 (m, 1H) 3.799 (m, 12H) 2.904 (d, J = 0.019, 4H) 2.228 (m, 1H) 2.0677(m, 2H) 514.6 (M+H)
16		515.6 (M+H)

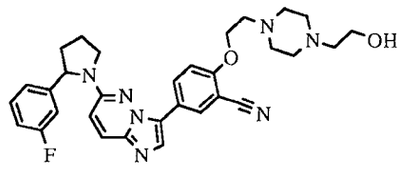
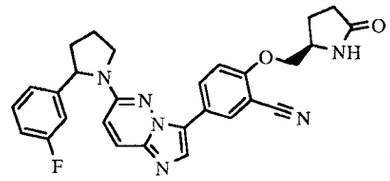
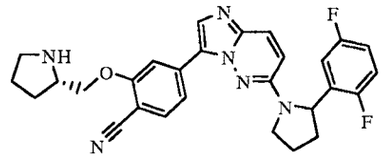
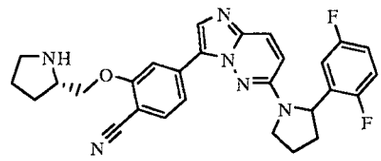
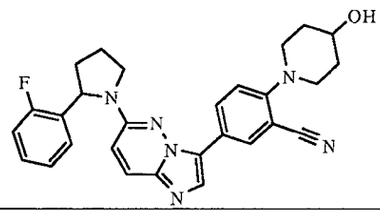
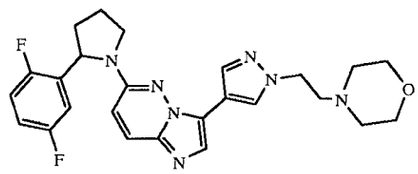
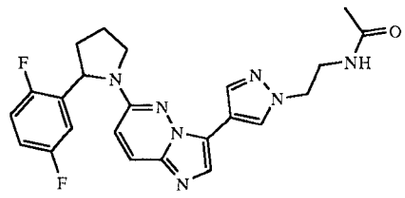
17		531.6 (M+H)
18		515.6 (M+H)
19		515.6 (M+H)
20		9.747 (br s, 1H) 8.280 (d, J = 0.009, 1H) 7.999 (m, 1H) 7.419 (m, 3H) 7.132 (m, 3H) 6.297 (br s, 1H) 5.313 (d, J = 0.019, 1H) 4.001 (m, 4H) 3.625 (m, 3H) 3.433 (m, 4H) 3.197 (m, 4H) 1.994 (m, 5H) 544.6 (M+H)
21		556.6 (M+H)
22		501.5 (M+H)

23		502.6 (M+H)
24		515.6 (M+H)
25		545.6 (M+H)
26		9..321 (m, 1Il) 8.935 (m, 1H) 8.365 (m,1H) 7.998 (m, 1H) 7.743 (m, 2H) 7.408 (m, 1H) 7.147 (m, 1H) 7.034 (m ,1H) 5.321 (d, J = 0.019, 1H) 4.530 (m, 2H) 4.371 (m, 2H) 4.048 (m, 2H) 3.674 (m, 1H) 3.281 (m, 2H) 2.216 (m ,1H) 2.072 (m, 3H) 1.947 (m, 3H) 501.5 (M+H)
27		546.6 (M+H)
28		9.774 (br s, 1H) 8.374 (s, 1H) 8.014 (m, 1H) 7.863 (m, 1H) 7.726 (m, 1H) 7.632 (m, 1H)7.453 (m, 1H) 7.152 (m, 1H) 7.047 (m, 1H) 5.327 (m, 2H) 5.203 (d, J = 0.02, 1H) 4.533 (m, 1H) 4.038 (m, 1H) 3.653 (m, 1H) 3.543 (m, 2H) 2.920 (m, 4H) 2.046 (m, 2H) 1.914 (m, 1H) 1.349 (d, J = 0.015, 2H)

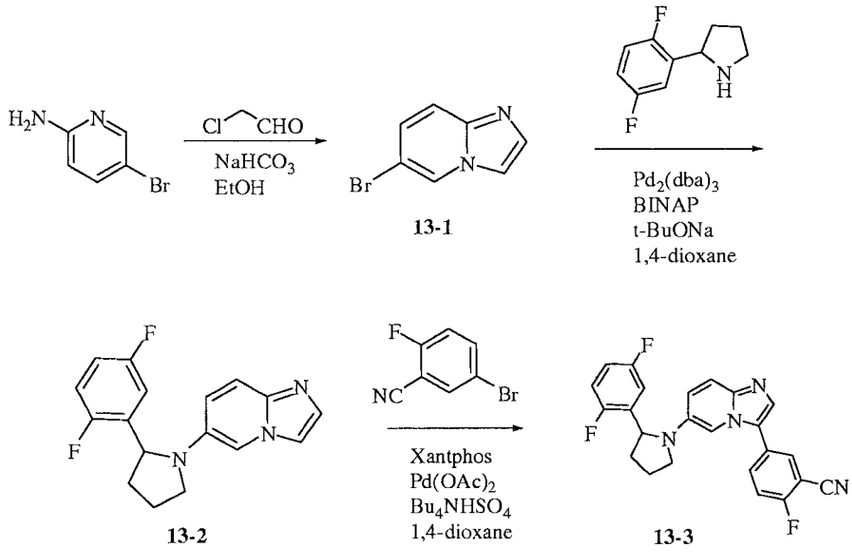
		503.6 (M+H)
29		9.584 (br s, 1H) 8.324 (s, 1H) 7.988 (m, 1H) 7.697 (m, 1H) 7.608 (m, 1H) 7.428 (m, 2H) 7.145 (m, 1H) 7.033 (m, 1H) 5.337 (d, J = 0.019, 1H) 4.342 (m, 3H) 4.041 (m, 2H) 3.644 (m ,3H) 3.415 (m, 1H) 3.132 (m, 1H) 2.922 (d, J = 0.013,, 2H) 2.334 (m, 1H) 2.036 (m, 6H) 1.829 (m, 1H) 529.6 (M+H)
30		519.6 (M+H)
31		9.973 (br s, 1H) 8.358 (m, 1H) 7.994 (m, 2H) 7.764 (m, 1H), 7.667 (m, 1H) 7.410 (m, 1H) 7.147 (m, 1H) 7.034 (m, 2H) 5.343 (d, J=0.02, 1H) 4.655 (m, 2H) 4.390 (m, 2H) 4.038 (m, 2H)3.657 (m, 2H) 3.191 (m, 1H) 2.334 (m, 1H) 2.122 (m, 5H) 515.6 (M+H)
32		8.367 (br d, 1H) 8.221 (d, J = 0.013, 1H) 7.952 (t, J = 0.024, 1H) 7.142 (m, 7H) 5.151 (dd, J = 0.016, 0.004, 1H) 3.930 (m, 2H) 3.738 (t, J = 0.011, 4H) 3.614 (t, J = 0.021, 2H) 3.174 (m, 3H) 1.977 (m, 2H) 1.826 (m, 1H) 469.5 (M+H)

33		482.6 (M+H)
34		526.6 (M+H)
35		512.6 (M+H)
36		552.7 (M+H)
37		497.6 (M+H)
38		511.6 (M+H)
39		482.6 (M+H)

40		497.6 (M+H)
41		513.6 (M+H)
42		595.7 (M+H)
43		553.6 (M+H)
44		553.7 (M+H)
45		483.6 (M+H)
46		554.7 (M+H)

47		556.6 (M+H)
48		497.5 (M+H)
49		501.5 (M+H)
50		501.5 (M+H)
51		483.6 (M+H)
52		480.5 (M+H)
53		452.5 (M+H)

Scheme 13



Example 13

5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-a]pyridin-3-yl)-2-fluorobenzonitrile

[000413] 5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-a]pyridin-3-yl)-2-fluorobenzonitrile (13-3) was synthesized in three steps as shown in scheme 13.

[000414] In step 13-1, chloracetaldehyde (55% in water, 0.27 mL, 4.5 mmol) and $NaHCO_3$ (143 mg, 1.7 mmol) were added to a solution of 5-bromopyridin-2-amine (173 mg, 1 mmol) in EtOH (7 mL). The mixture was heated to reflux and continued overnight. The reaction mixture was cooled to room temperature and concentrated under vacuum. Dichloromethane was added to extract the residue. The organic layer was washed with water, brine, dried over Na_2SO_4, filtered, and evaporated to give the crude product. The crude was purified column chromatography (Silica gel, EtOAc/Hexane, gradient) to give 6-bromoimidazo[1,2-a]pyridine (13-1).

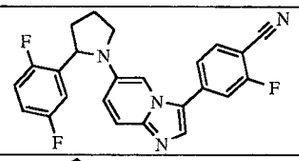
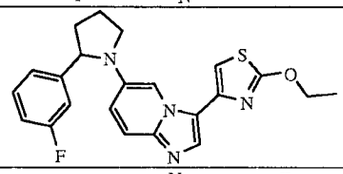
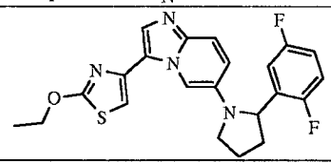
[000415] In step 13-2, a microwaveable vial was charged with 6-bromoimidazo[1,2-a]pyridine (197 mg, 1 mmol), 2-(2,5-difluorophenyl)pyrrolidine (238 mg, 1.3 mmol), $Pd_2(dba)_3$ (18 mg, 0.02 mmol), BINAP (50 mg, 0.08 mmol), t-BuONa (135 mg, 1.4 mmol) and 1,4-dioxane (5 ml), and the mixture was heated to 120 °C for 30 minutes using microwave irridiation. The mixture was filtered through celite. The filtrate was concentrated and purified by column chromatography (Silica gel, EtOAc/hexane, gradient) to give 6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-a]pyridine (13-2).

[000416] In step 13-3, a sealed vial was charged with 6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-a]pyridine (30 mg, 0.1 mmol), 5-bromo-2-fluorobenzonitrile (20 mg, 0.1 mmol), $Pd(OAc)_2$ (1 mg, 0.005 mmol), Xantphos (6 mg, 0.01 mmol), Cs_2CO_3 (49 mg, 0.15 mmol) , Bu_4NHSO_4 (3 mg, 0.01

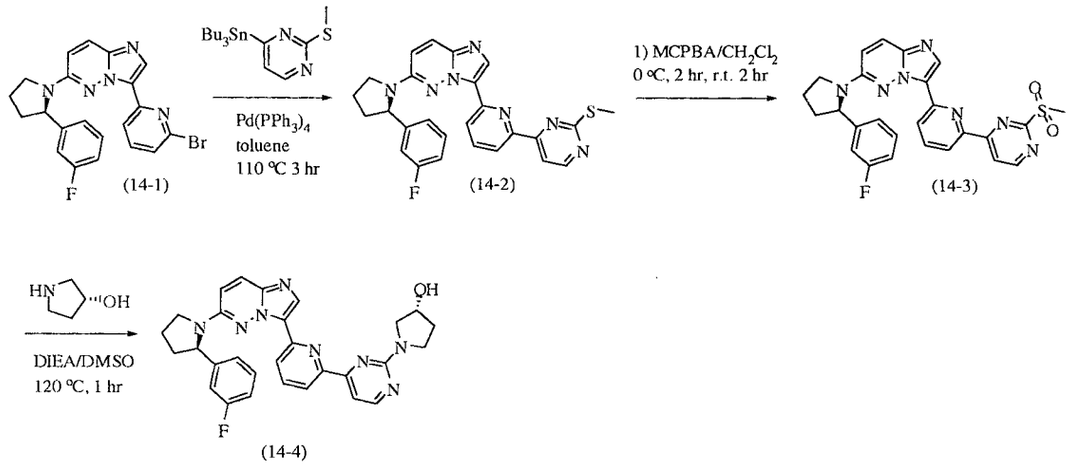
mmol) and 1,4-dioxane (0.5 ml), and the mixture was heated to 90 °C overnight. The mixture was filtered through celite. The filtrate was concentrated and purified by preparative LC-MS to give 5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-a]pyridin-3-yl)-2-fluorobenzonitrile (12-3). LC-MS: 419.2 (MH^+).

[000417] By repeating the procedures described in example 13, using appropriate starting materials, the following compounds of Formula I, as identified in Table 6, were obtained.

Table 6

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
1		419.1 (M+H)
2		427.2 (M+H)
3		409.2 (M+H)

Scheme 14



Example 14

[000418] (R)-1-(4-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)pyrrolidin-3-ol (14-4) was synthesized in three steps as shown in scheme 14.

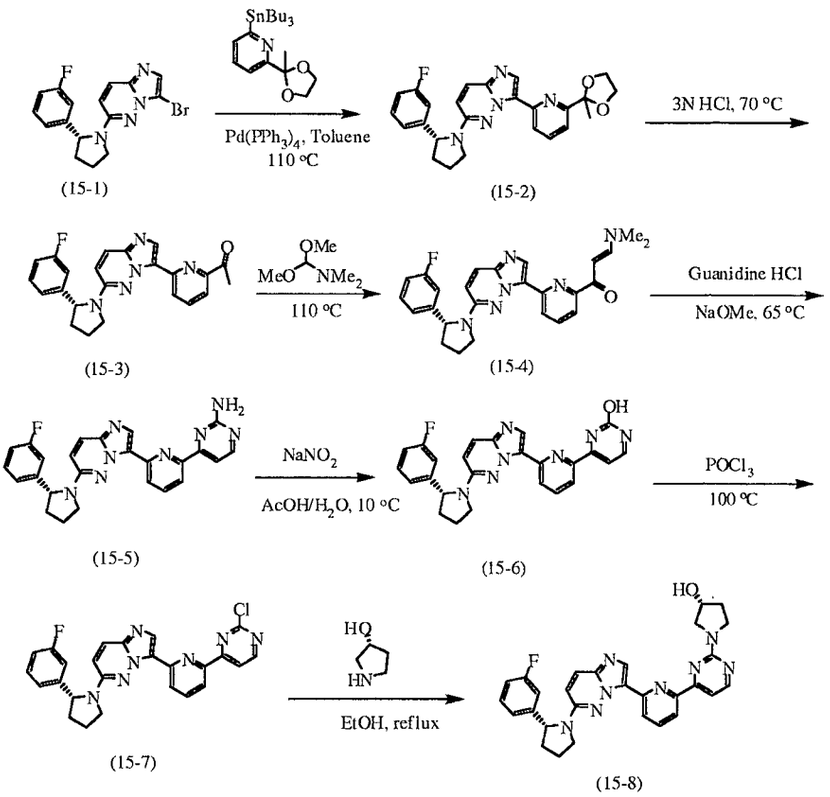
[000419] In step 14-1, 2-(methylthio)-4-(tributylstannyl)pyrimidine (4.3 g, 13.2 mmol) and $Pd(PPh_3)_4$ (196 mg, 0.17 mmol) were added to a solution of (R)-3-(6-bromopyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine (14-1) (1.5 g, 3.4 mmol) in toluene (35 mL). The mixture was degassed using N_2 for 15 minutes and then heated at 110 °C for 2 hours. All the solvents were removed. The resulting mixture was purified by column chromatography (silica gel, EtOAc/CH_3OH, 0 to 10% gradient) to give (R)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(2-(methylthio)pyrimidin-4-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine (14-2) as a light-yellow foam. LC/MS: 484.2 (MH+).

[000420] In step 14-2, a solution of MCPBA (720 mg, 3.2 mmol) in CH_2Cl_2 (15 mL) was added slowly to a solution of (R)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(2-(methylthio)pyrimidin-4-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine (14-2) (776 mg, 1.6 mmol) in CH_2Cl_2 (16 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour and then warmed to room temperature. The mixture was then stirred at room temperature for 2 hours. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with 1N NaOH (75 mLx2) and brine (75 mLx2). The organic layer was separated, dried over Na_2SO_4 and concentrated. The mixture was purified by column chromatography (silica gel, CH_2Cl_2/CH_3OH, 2 to 5% gradient). (R)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(2-(methylsulfonyl)pyrimidin-4-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine (14-3) was obtained as a light yellow solid. LC/MS: 516.2 (MH+). Also obtained was 6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(2-(methylsulfinyl)pyrimidin-4-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine.

[000421] In step 14-3, (R)-pyrrolidin-3-ol (136 mg, 1.56 mmol) and DIEA (453 uL, 2.6 mmol) were added to a solution of (R)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(2-(methylsulfonyl)pyrimidin-4-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine (14-3) (268 mg, 0.52 mmol) in DMSO (3 mL). The mixture was

heated to 120 °C for 1 hour. The mixture was diluted with CH_2Cl_2, washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated. The mixture was purified by column chromatography (silica gel, CH_2Cl_2/CH_3OH, 5% gradient) to give (R)-1-(4-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)pyrrolidin-3-ol (14-4). LC/MS: 523.2 (MH+).

Scheme 15



Example 15

[000422] (R)-1-(4-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)pyrrolidin-3-ol was also synthesized in seven steps as shown in scheme 15.

[000423] In step 15-1, 2-(2-methyl-1,3-dioxolan-2-yl)-6-(tributylstannyl)pyridine (57 g, 124 mmol) in 100 mL of toluene was cannula transferred under the argon atmosphere to a suspension of 3-bromo-6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine (15-1) (30 g, 83 mmol) and tetrakis(triphenylphospine)palladium (4.8 mg, 4.15 mmol) in 500 mL of toluene. The resulting reaction mixture was heated to 110 °C for overnight. The reaction progress was monitored by LC/Mass. After the reaction was complete, the reaction vessel was cooled to room temperature and the solvent reduced to 1/3 of the original volume. The purification was performed by flash chromatography using pure ethyl acetate to afford (*R*)-6-(2-(3-fluorophenyl) pyrrolidin-1-yl)-3-(6-(2-methyl-1,3-dioxolan-2-yl) pyridine-2-

yl)imidazo[1,2-b]pyridazine (15-2). ^{1}H NMR (400 MHz, DMSO-d6) δ 8.10 (s, 1H), 8.09 (s br, 1H), 7.93 (d, 1H, J = 9.6 Hz), 7.72 (m, 1H), 7.39 (m, 2H), 7.18 (m, 2H), 7.04 (m, 1H), 6.89 (br s, 1H), 5.16 (d, 1H, J = 8.0 Hz), 4.02 (m, 3H), 3.91 (m, 2H), 3.68 (m, 2H), 2.48 (m, 1H), 2.05 (m, 2H), 1.88 (m, 1H), 1.69 (s, 3H). LCMS: *m/z* 446.2 (M+1).

[000424] In step 15-2, (*R*)-6-(2-(3-fluorophenyl) pyrrolidin-1-yl)-3-(6-(2-methyl-1,3-dioxolan-2-yl) pyridine-2-yl)imidazo[1,2-b]pyridazine (15-2) (30g, 67.4 mmol) was charged with mixture of THF (150 mL) and 2N HCl (450 mL) and the resulting solution was heated to 70 °C overnight. LC/MS was used to confirm the reaction was complete. The reaction mixture was then neutralized using 10N NaOH resulting in the formation of (*R*)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazole[1,2-b]pyridazin-3-yl)pyridine-2-yl)ethanone (15-3) as a pale yellow precipitate which was filtered and dried (Note: that the product needs to be dry for step 15-3 as any amount of water makes the reaction sluggish). 1H NMR: ppm 8.52 (s, 1H), 8.32 (br s, 1H), 8.10 (d, 1H, J = 10 Hz), 7.96 (br s, 1H), 7.87 (d, 1H, J = 7.6 Hz), 7.41 (m, 1H), 7.20 (m, 3H), 7.05 (m, 1H), 5.23 (dd, 1H, J = 8.2 Hz, 2 Hz), 4.06 (m, 1H), 3.72 (q, 1H, J = 8.0 Hz), 2.71 (s, 3H), 2.51 (m, 1H), 2.07 (m, 2H), 1.91 (m, 1H). LCMS: *m/z* 446.2(M+1)

[000425] In step 15-3, a mixture of (*R*)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazole[1,2-b]pyridazin-3-yl)pyridine-2-yl)ethanone (15-3) (25g, 62.3 mmol) and dimethylforamide dimethylacetal (300 mL) was heated overnight at reflux and then cooled to room temperature. The volatiles were removed by rotary evaporation under reduced pressure and the residual solids were triturated with 200 mL of the mixture of EtOAc/Hexane (1: 5) and filtered to give (*R,E*)-3-(dimethylamino)1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazole[1,2-b]pyridazin-3-yl)pyridine-2-yl)prop-2-en-1-one (15-4) as a yellow solid which was used in the next step without further purification.

[000426] In step 15-4, freshly prepared sodium methoxide in methanol (400 mL) was cannula transferred to a solution of (*R,E*)-3-(dimethylamino)1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazole[1,2-b]pyridazin-3-yl)pyridine-2-yl)prop-2-en-1-one (15-4) and guanidine HCl in methanol (200 mL). The resulting suspension was heated overnight at 65 °C. The reaction progress was monitored by LC/Mass. After the reaction was complete, the reaction mixture was neutralized with 4N aqueous HCl and then stirred for 1 hour at room temperature. The reaction mixture was filtered to give (R)-4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-amine (15-5) as a yellow solid. 1H NMR: ppm 8.42 (d, 1H, J = 4.8 Hz), 8.31 (s, 1H), 8.16 (d, 1H, J = 8.0 Hz), 7.96 (d, 1H, J = 10 Hz), 7.89 (m, 1H), 7.64 (d, 1H, J = 4.8 Hz), 7.42 (ddd, 1H, J = 8.0, 8.0, 6.0 Hz), 7.20 (m, 2H), 7.05 (ddd, 1H, J = 8.4, 8.4, 2.0 Hz), 6.91 (br s, 1H), 6.76 (s, 2H), 5.22 (dd, 1H, J = 8.2 Hz, 2.4 Hz), 4.03 (m, 1H), 3.70 (q, 1H, J = 8.4 Hz), 2.51 (s, 1H), 2.06 (m, 2H), 1.90 (m, 1H), 1.18 (d, 1H, J = 6.4Hz). LCMS: *m/z* 453.2(M+1).

[000427] In step 15-5, an aqueous solution of sodium nitrite ($NaNO_2$) was added dropwise to a solution of (R)-4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-

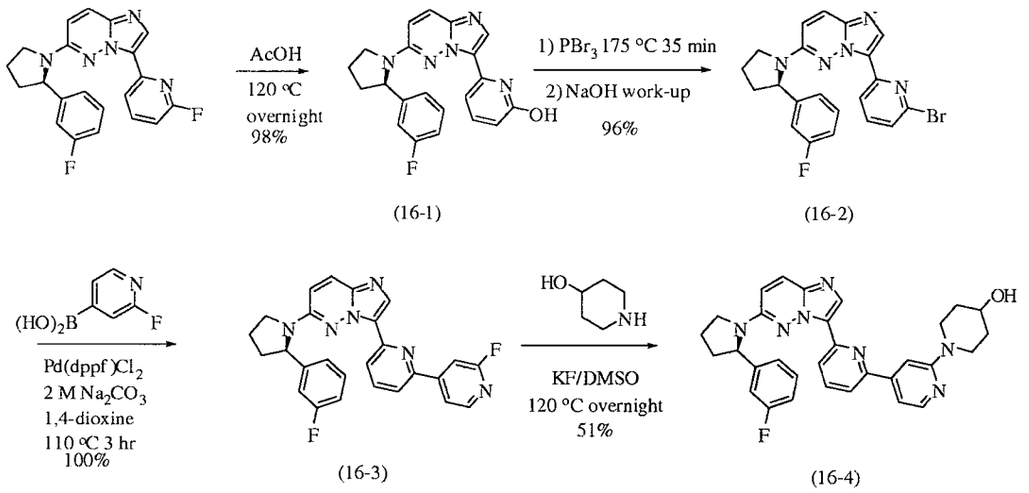
amine (15-5) (20g, 44.2 mmol) in AcOH (250 mL) and H_2O (250 mL) while maintaining the temperature between 5 °C and 10 °C. The reaction progress was monitored by LC/MS. After the reaction was complete, the solvents were concentrated to dryness and the residue was then treated with K_2CO_3 in methanol. The resulting mixture was then neutralized with 3N HCl, the solvent concentrated and the mixture then extracted with dichloromethane (X3). The extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography (10 % MeOH in CH_2Cl_2 with increasing amounts of methanol to 15%) to afford (*R*)-4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazole[1,2-b]pyridazin-3-yl)pyridine-2-yl)pyrimidin-2-ol (15-6) as a yellow solid. 1H NMR: ppm 12.1 (s, 1H), 8.32 (s, 1H), 8.16 (d, 1H, J = 8.0 Hz), 7.95 (d, 1H, J = 10 Hz), 7.90 (m, 1H), 7.49 (d, 1H, J = 6.4 Hz), 7.42 (ddd, 1H, J = 8.0, 8.0, 6.4 Hz), 7.20 (m, 2H), 7.05 (ddd, 1H, J = 8.4, 8.4, 2.4 Hz), 6.91 (br s, 1H), 5.2 (dd, 1H, J = 8.2 Hz, 2.4 Hz), 4.02 (m, 1H), 3.69 (q, 1H, J = 8.0 Hz), 2.49 (m, 2H), 2.05 (m, 2H), 1.89 (m, 1H). LCMS: 454.2(M+1).

[000428] In step 15-6, (*R*)-4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazole[1,2-b]pyridazin-3-yl)pyridine-2-yl)pyrimidin-2-ol (15-6) (15g, 33.2 mmol) was charged with $POCl_3$ (200 mL) and then heated overnight at 100 °C. The reaction progress was monitored by LC/MS. After the reaction was complete, the volatile residuals were removed by distillation under reduced pressure. After the removal of most of the $POCl_3$, the resultant solids were dissolved with dichloromethane and neutralized with aqueous K_2CO_3. The organic solvents were dried over Na_2SO_4, filtered and concentrated with rotary evaporator under reduced pressure to give crude yellow solids which were purified by column chromatography (5% MeOH in CH_2Cl_2) to give (*R*)-3-(6-(2-chloropyrimidin-4-yl)pyrimidin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazole[1,2-b]pyridazine (15-7) as a yellow solid. 1H NMR: ppm 8.93 (d, 1H, J = 4.8 Hz), 8.58 (d, 1H, J = 2.8 Hz), 8.41 (s, 1H), 8.34 (ba s, 1H), 8.22 (d, 1H, J = 8.0 Hz), 7.95 (m, 2H), 7.41 (ddd, 1H, J = 8.0, 8.0, 6.4 Hz), 7.20 (m, 2H), 7.05 (ddd, 1H, J = 8.4, 8.4, 2.4 Hz), 6.92 (br s, 1H), 5.21 (dd, 1H, J = 8.2 Hz, 2.4 Hz), 4.03 (m, 1H), 3.70 (q, 1H, J = 8.0 Hz), 2.47 (m, 2H), 2.06 (m, 2H), 1.90 (m, 1H). LCMS: 472.2(M+1).

[000429] In step 15-7, (R)-3-hydroxy pyrrolidine was added to a solution of the (*R*)-3-(6-(2-chloropyrimidin-4-yl)pyrimidin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazole[1,2-b]pyridazine (15-7) (10g, 21.2 mmol) in ethanol (100 mL) and the resulting mixture was heated at reflux for 7 hours. The volatile residuals were removed by rotary evaporator under reduced pressure followed by column chromatography to give (R)-1-(4-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)pyrrolidin-3-ol as a pale yellow solid. 1H NMR: ppm 8.51 (d, 1H, J = 5.2 Hz), 8.32 (s, 1H), 8.30 (br s, 1H), 8.24 (d, 1H, J = 7.6 Hz), 7.93 (d, 1H, J = 10 Hz), 7.86 (m, 1H), 7.65 (d, 1H, J = 4.8 Hz), 7.40 (ddd, 1H, J = 8.0, 8.0, 6.4 Hz), 7.20 (s, 1H), 7.17 (m, 1H), 7.04 (ddd, 1H, J = 8.4, 8.4, 2.4 Hz), 6.85 (br s, 1H), 5.17 (dd, 1H, J = 8.2 Hz, 2.4 Hz), 5.01 (d, 1H, J = 3.2 Hz), 4.43 (br s, 1H), 4.02 (m, 1H), 3.65 (m, 5H), 2.45 (m, 1H), 2.05 (m, 3H), 1.89 (m, 2H). 13C NMR: ppm 163.58, 162.17, 161.16,

160.15, 159.14, 153.65, 151.80, 147.53, 147.13(d, J =25.6 Hz), 137.66, 133.20, 130.39(d, J = 30.4 Hz), 126.44, 126.06, 121.64, 120.67, 118.52, 113.45 (d, J = 83.2 Hz), 112.40 (d, J = 87.6 Hz), 110.31, 104.90, 69.10, 61.26, 54.82, 48.39, 44.42, 35.27, 33.47, 22.66. LCMS: 523.2 (M+1).

Scheme 16



Example 16

[000430] (R)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)piperidin-4-olwas synthesized in four steps as shown in scheme 16.

[000431] In step 16-1, a suspension of (R)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-fluoropyridin-2-yl)imidazo[1,2-b]pyridazine (16 g, 42 mmol) in acetic acid (150 mL) was heated overnight at 120 °C (approx. 20 hours). The suspension turned clear after heating. The mixture was concentrated under vacuum to give a brown oil. The oil was dissolved in CH_2Cl_2 (750 mL) and washed with saturated $NaHCO_3$ (300mLx3), brine (300mLx2). The organic layer was separated, dried over (Na_2SO_4) and concentrated to give 15.5 g of the crude (R)-6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-ol (16-1) which was used in the next step without further purification. LC/MS: 376.2 ($M+H^+$).

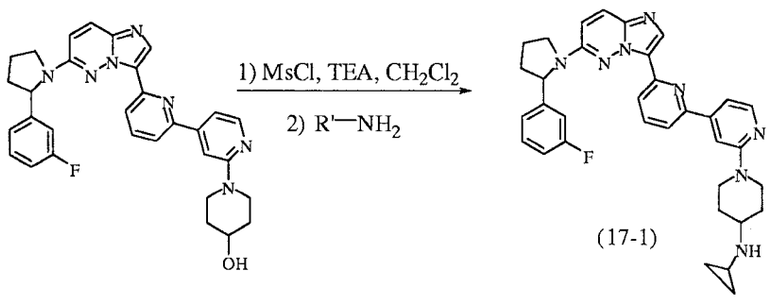
[000432] In step 16-2, a suspension of crude (R)-6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-ol (16-1) (13.3 g, 35.4 mmol) in PBr_3 (25 mL) was heated to 175 °C for 35 minutes. While the mixture was hot, it was poured into ice-cold 2N NaOH (1.2 L). The solid was collected by filtration and washed with H_2O. The final product was dried under high vacuum overnight to give (R)-3-(6-bromopyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine (16-2) as a light-yellow solid which was used in the next step without further purification. LC/MS: 438.2 ($M+H^+$).

[000433] In step 16-3, 2-fluoropyridin-4-ylboronic acid (97%) (9.6 g, 66 mmol), $Pd(dppf)Cl_2$ (1.3 g, 1.65 mmol) and 2N Na_2CO_3 (50 mL, 99 mmol) were added to a suspension of (R)-3-(6-bromopyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine (16-2) (14.5 g, 33 mmol) in 1,4-dioane (250 mL). The mixture was degassed for 15 minute using N_2 and then heated at 110 °C for 3 hours. The mixture was

filtered through a celite pad and rinsed with ethyl acetate (EtOAc). The filtrate was washed with brine, dried over Na_2SO_4, and concentrated to give (R)-3-(2'-fluoro-2,4'-bipyridin-6-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine (16-3) as a dark oil, which was used in the next step without further purification. LC/MS: 455.2 ($M+H^+$).

[000434] In step 16-4, potassium fluoride (10 g, 175 mmol) and 4-hydroxypiperidine (10.6 g, 105 mmol) were added to a solution of crude (R)-3-(2'-fluoro-2,4'-bipyridin-6-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine (16-3) (16.1 g, 35 mmol) in DMSO (100 mL). The mixture was heated overnight to 120 °C (approx. 14 hours). The mixture was filtered through a celite pad and rinsed with EtOAc (1 L). The filtrate was washed with brine, dried over Na_2SO_4, filtered and concentrated to give a dark oil. The mixture was purified by column chromatography (silica gel, CH_2Cl_2/CH_3OH, gradient 5% to 15%) to yield (R)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)piperidin-4-ol (16-4) which was crashed out from CH_2Cl_2, filtered and dried under high vacuum. ^1H NMR (400 MHz, DMSO, ppm): δ 8.30 (s, 1H), 8.22 (d, 1H, J=5.2 Hz), 8.10-8.24 (bs, 1H), 7.90-7.98 (m , 2H), 7.76-7.86 (bs, 1H), 7.52 (s, 1H), 7.40 (q, 1 H, J=7.4 Hz), 7.34 (d, 1H, J=5.2 Hz), 7.04 (t, 1H, J=8 Hz), 6.80-6.94 (bs, 1H), 5.19 (d, 1H, J=8 Hz), 4.71 (d, 1H, J=4 Hz), 4.10-4.18 (m, 2H), 3.93-4.06 (m, 1H), 3.65-3.75 (m, 2H), 3.10-3.20 (m, 2H), 1.98-2.10 (m, 2H), 1.78-1.92 (m, 3H), LC/MS: 536.2 ($M+H^+$), 1.34-1.45 (m, 2H). ^{13}C NMR (400 MHz, DMSO, ppm): 163.53, 161.11, 159.53,153.95, 151.76, 148.27 (d, J=34.7 Hz), 147.69, 147.10 (d, J=25.6 Hz), 146.92, 137.61, 133.14 (d, J=23.2 Hz), 130.34 (d, J=32.4 Hz), 126.54, 126.04, 121.56, 119.26, 118.75, 113.40 (d, J=83.6 Hz), 112.41 (d, J=86.0), 110.26, 109.86, 103.75, 66.34, 61.24, 48.37, 42.72, 35.12, 33.71, 22.65.

Scheme 17



Example 17

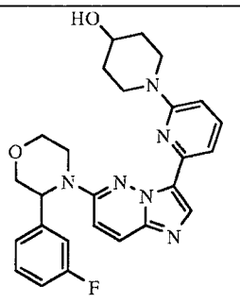
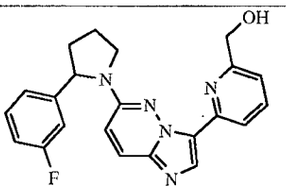
[000435] (N-cyclopropyl-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)piperidin-4-amine) (17-1) was synthesized as shown in scheme 17.

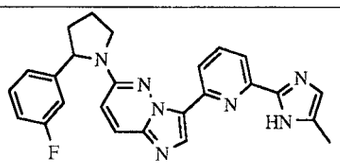
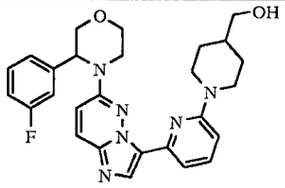
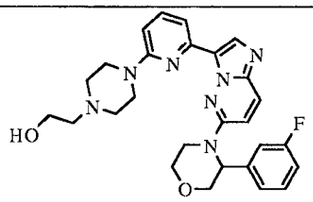
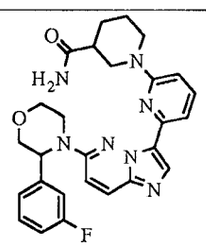
[000436] (N-cyclopropyl-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)piperidin-4-amine) was prepared in the following manner. To a 20 mL reaction flask was added 1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)piperidin-4-ol (30 mg, 0.056 mmol) and 0.8mL of methylene chloride. This solution was charged with

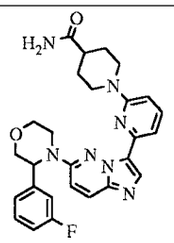
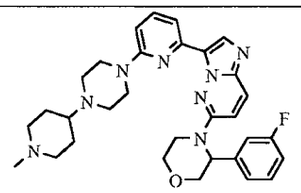
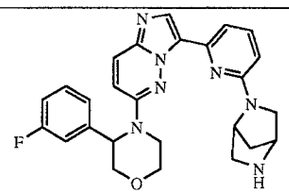
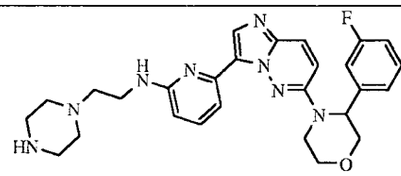
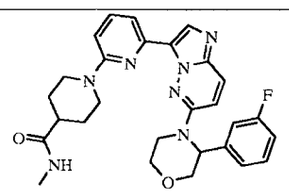
triethylamine (0.10 mL, 0.69 mmol) and dropwise addition of methane sulfonyl chloride (MsCl, approx. 20 mg, 0.18 mmol). The resulting solution was stirred for 2 hours, followed by quenching with water, ethyl acetate extraction (3 x 30 mL), and the organic extracts were transferred to a 10 mL volume resealable vessel. The residue in the vessel was charged with 2 mL cyclopropylamine (excess, co-solvent) and 0. 5 mL of THF. The vessel was sealed and heated for 6 hours at 90 °C. Upon cooling, the contents of the vessel were concentrated to a volume of 1 mL and directly subjected to reverse phase separation (gradient, C-18 support, 10 to 70 %, acetonitrile:water) to give (N-cyclopropyl-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)piperidin-4-amine). ^{1}H NMR (400 MHz, D_3 acetonitrile) δ ppm 8.71 (br s, 1H), 8.41(s, 1H) 8.26 (d, J = 7.2 Hz, 1H), 7.99 (app d, J = 6.7 Hz, 2H), 7.85 (d, J = 6.2 Hz, 1H), 7.73 (br s, 1H), 7.63 (s, 1H), 7.42 (d, J = 6.4 Hz, 1H), 7.39 (app q, J = 6.8 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.05 (dt, J = 8.6, 1.9 Hz, 1H), 6.99-6.82 (m, 1H), 5.27 (d, J = 6.4 Hz, 1H), 4.54 (app d, J = 10 Hz, 2H), 4.00 (app q, J = 3.9 Hz, 1H), 3.69-3.62 (m, 1H), 3.46 (app d, J = 5.8 Hz, 1H), 2.98 (app q, J = 4.2 Hz, 2H), 2.73 (br s, 2H), 2.47-2.35 (m, 1H), 2.13 (app dd, J = 5.6 Hz, 2H), 2.08-2.03 (m, 2H),1.89-1.86 (m, 1H), 0.82-0.66 (m, 5H). LRMS observed *m/z* 575.3 major ion (calcd for M+H, 575.3).

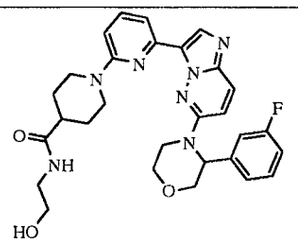
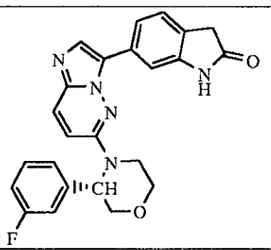
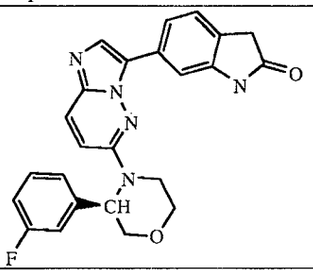
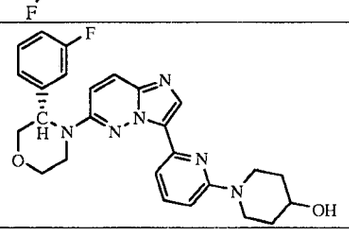
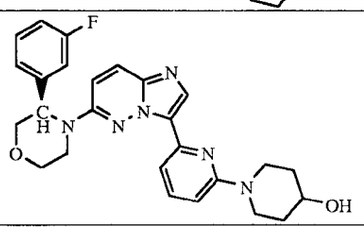
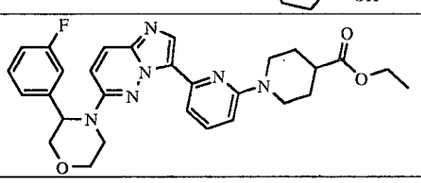
[000437] Additional representative compounds of Formula (I), prepared following the procedures described above, were set forth in Table 7.

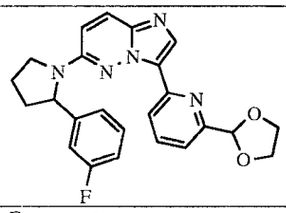
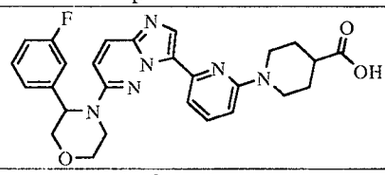
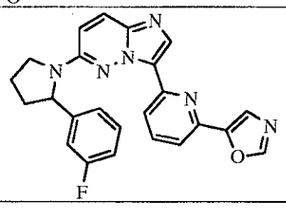
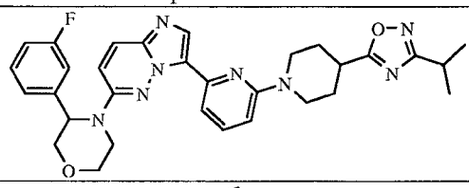
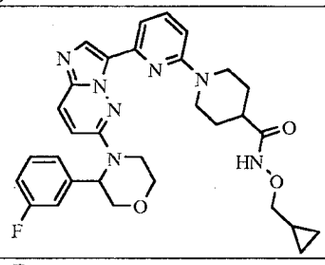
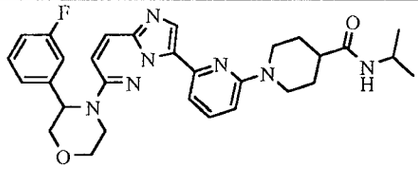
Table 7

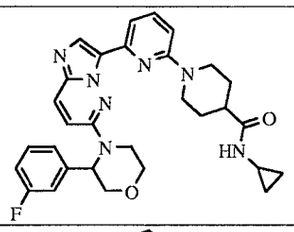
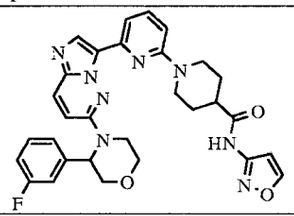
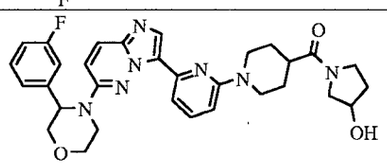
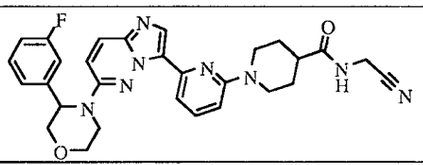
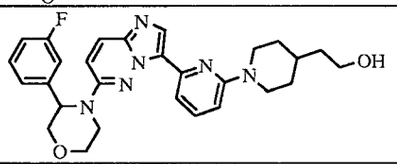
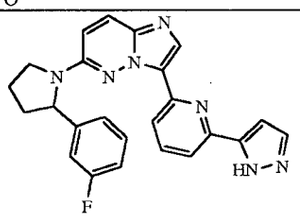
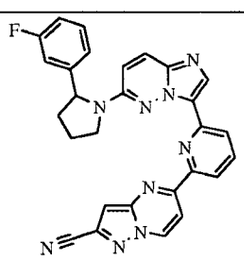
Compound Number	**Structure**	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
1		^{1}H NMR (400 MHz, MeOH-d4) d 7.99 (s, 1H), 7.71(d, 1H, J = 10.0 Hz), 7.46 (m, 2H), 7.19 (m, 1H), 7.11 (m, 3H), 6.83 (m, 1H), 6.65 (d, 1H, J = 8.0 Hz), 5.01 (t, 1H, J = 3.6 Hz), 4.10 (m, 3H), 4.00 (m, 2H), 3.77 (m, 3H), 3.59 (m ,1H), 3.03 (m, 1H), 1.91 (s, 1H), 1.84 (m, 2H), 1.44 (m, 2H) MS (m/z): 474.53
2		MS (m/z): 389.42

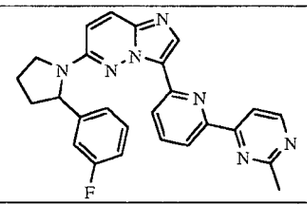
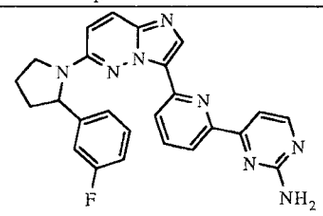
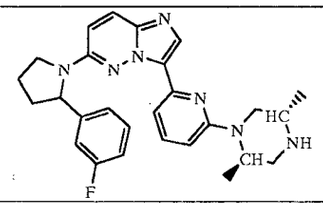
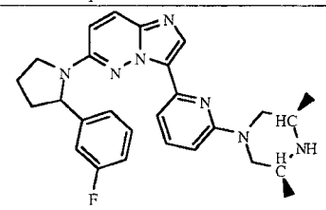
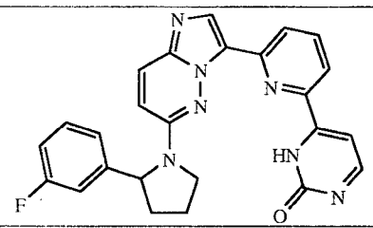
3		MS (m/z): 439.49
4		^{1}H NMR (400 MHz, CHCl3-d3) d 8.54(d, 1H, J = 10.0 Hz), 8.23 (s, 1H), 7.46 (m, 2H), 7.23 (m, 1H), 7.12 (d, 1H, J = 10.4 Hz), 7.05 (m, 2H), 6.91 (m, 1H), 6.65 (m , 1H), 5.09 (t, 1H, J = 2.8 Hz), 4.34 (m ,2H), 4.24 (dd, 1H, J = 12.0, 2.0 Hz), 4.12 (dt, 1H, J = 11.2, 2.8 Hz), 4.05 (dd, 1H, J = 12.8, 3.6 Hz), 3.92 (dt, 1H, J = 12.8, 2.8 Hz), 3.82 (ddd, 1H, J = 11.2, 11.2, 3.2 Hz), 3.65 (m ,2H), 3.48 (d, 2H, J = 6.0 Hz), 3.30 (brs, 1H), 2.82 (ddd, 1H, J = 12.4, 12.4, 1.6 Hz), 1.73 (m, 1H), 1.24 (m, 3H), 0.80 (m, 1H) MS (m/z): 488.56
5		^{1}H NMR (400 MHz, CHCl3-d3) d 8. 41(d, 1H, J = 10.0 Hz), 8.20 (s, 1H), 7.64 (d, 1H, J = 7.6 Hz), 7.58 (t, 1H, J = 8.0 Hz), 7.24 (m, 1H), 7.13 (d, 1H, J = 10.0 Hz), 7.05 (m, 1H), 6.91 (m, 1H), 6.67 (d, 1H, J = 8.4 Hz), 5.09 (t, 1H, J = 2.8 Hz), 4.23 (dd, 2H, J = 12.0, 2.4 Hz), 4.12 (dt, 2H, J = 12.8, 3.2 Hz), 4.05 (dd, 2H, J = 12.0, 4.0 Hz), 3.99 (m, 3H), 3.90 (dt, 2H, J = 13.2, 2.8 Hz), 3.82 (ddd, 2H, J = 10.4, 10.4, 3.2 Hz), 3.66 (m ,3H), 3.17(m, 3H) MS (m/z): 503.57
6		MS (m/z): 501.55

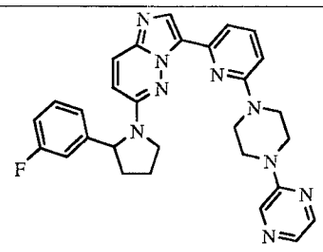
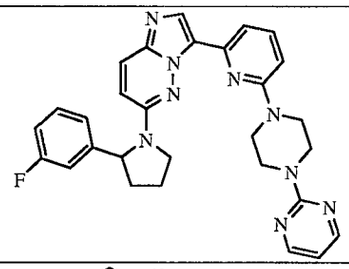
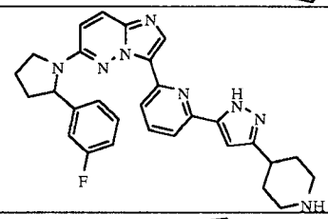
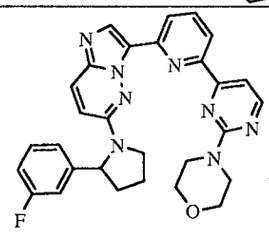
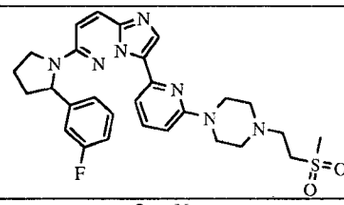
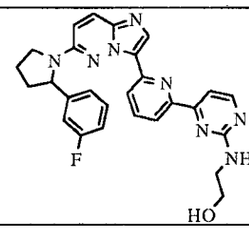
7		MS (m/z): 501.55
8		MS (m/z): 556.68
9		^{1}H NMR (400 MHz, MeOH-d4) d 8.19 (s, 1H), 7.74(d, 1H, J = 10.0 Hz), 7.51 (t, 1H, J = 8.8 Hz), 7.42 (ddd, 1H, J = 8.0, 8.0, 2.8 Hz), 7.17 (m, 1H), 7.08 (m, 2H), 6.84 (ddd, 1H, J = 8.4, 8.4, 2.0 Hz), 6.76 (d, 1H, J = 9.6 Hz), 6.23 (d, 1H, J = 8.0 Hz), 5.00 (m, 1H), 4.11 (dd, 1H, J = 13.2, 3.2 Hz), 4.03 (m, 2H), 3.80 (m, 3H), 3.59 (m ,2H), 3.28 (d ,1H, J = 9.6 Hz), 3.08 (s, 2H), 1.85 (m, 1H) MS (m/z): 471.53
10		MS (m/z): 502.59
11		^{1}H NMR (400 MHz, MeOH-d4) d 8.10 (s, 1H), 7.82(d, 1H, J = 10.0 Hz), 7.57(m, 2H), 7.32 (m, 1H), 7.20 (m, 3H), 6.91(m, 1H), 6.76 (d, 1H, J = 8.40 Hz), 5.22 (t, 1H, J = 3.2 Hz), 4.49 (d ,2H, J = 13.2 Hz), 4.20 (dd, 1H, J = 12.0, 3.2 Hz), 4.11 (m, 2H), 3.90 (m, 2H), 3.70 (m, 1H), 2.88 (ddd ,2H, J = 12.4, 12.4, 2.4 Hz), 2.72 (s, 3H), 2.72 (s, 1H), 1.84 (m, 2H), 1.74 (m, 2H) MS (m/z): 515.58

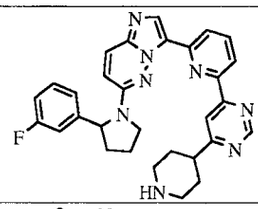
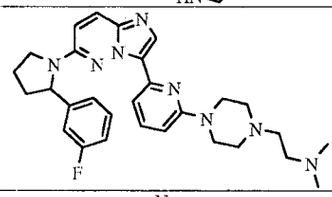
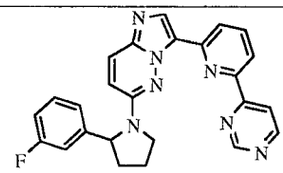
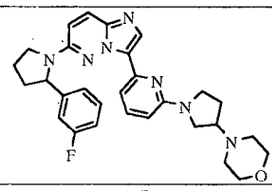
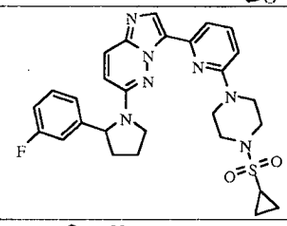
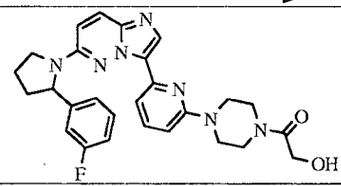
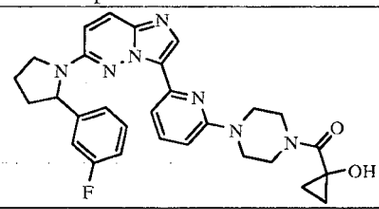
12		^{1}H NMR (400 MHz, MeOH-d4) d 8.18 (s, 1H), 7.73(d, 1H, J = 10.0 Hz), 7.53(d, 1H, J = 7.6 Hz), 7.45 (t, 1H, J = 8.0 Hz), 7.17 (m, 1H), 7.07(m, 2H), 6.84 (m, 1H), 6.76 (d, 1H, J = 8.0 Hz), 6.54 (d, 1H, J = 8.4 Hz), 6.16 (t, 1H, J = 4.2 Hz), 5.00 (t, 1H, J = 3.6 Hz), 4.38 (d ,2H, J = 12.4 Hz), 4.11 (dd, 1H, J = 12.0, 3.6 Hz), 4.03 (m, 2H), 3.80 (m, 2H), 3.66 (t, 2H, J = 4.8), 3.60 (m, 1H), 3.37 (m ,1H), 2.83 (m, 2H), 2.31 (m, 1H), 1.80 (m, 2H), 1.74 (m, 2H), 1.18 (m, 1H) MS (m/z): 545.61
13		MS (m/z): 429.45
14		MS (m/z): 429.45
15		MS (m/z): 474.53
16		MS (m/z): 474.53
17		MS (m/z): 530.59

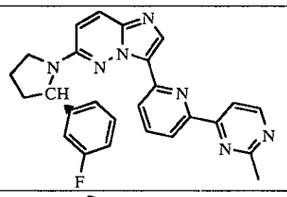
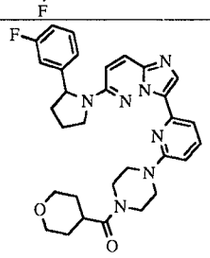
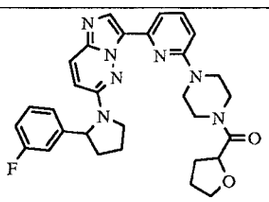
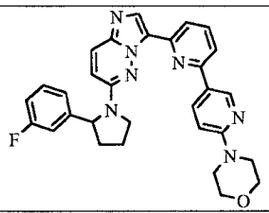
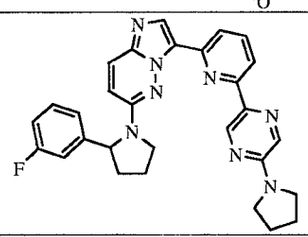
18		MS (m/z): 431.46
19		MS (m/z): 502.54
20		MS (m/z): 426.45
21		MS (m/z): 568.64
22		MS (m/z): 571.65
23		^{1}H NMR (400 MHz, DMSO-d6) d 8.12 (s, 1H), 8.09 (d, 1H, J = 6.0 Hz), 7.67 (d, 1H, J = 7.6 Hz), 7.56 (m, 2H), 7.09 (m, 4H), 7.04 (ddd, 1H, J = 8.4, 8.4, 2.4 Hz), 6.78 (d, 1H, J = 8.0 Hz), 5.30 (s, 1H), 4.40 (d, 2H, J = 11.6 Hz), 4.19 (dd, 1H, J = 12.0, 2.0 Hz), 4.02 (m, 3H), 3.80 (m, 2H), 3.60 (m, 1H), 2.82 (t, 2H, J = 12.0 Hz), 2.34 (m, 1H), 1.70 (m, 2H), 1.56 (m, 2H), 1.03 (d, 6H, J = 6.4 Hz) MS (m/z): 543.64

24		MS (m/z): 541.62
25		MS (m/z): 568.60
26		MS (m/z): 571.65
27		MS (m/z): 540.59
28		MS (m/z): 502.58
29		^{1}H NMR (400 MHz, MeOH-d4) d 8.33 (s, 1H), 8.03 (s br, 1H), 7.75 (d, 1H, J = 9.6 Hz), 7.60 (m, 2H), 7.46 (d, 1H, J = 7.6 Hz), 7.26 (m, 1H), 7.09 (d, 1H, J = 7.6 Hz), 6.91 (m, 2H), 6.73 (d, 1H, J = 2.0 Hz), 6.55 (d, 1H, J = 10.0 Hz), 5.03 (dd, 1H, J = 8.0, 2.4 Hz), 3.91 (m, 1H), 3.68 (q, 1H, J = 8.8 Hz), 2.44 (m, 1H), 2.06 (m ,2H), 1.97 (m, 2H) MS (m/z): 425.46
30		^{1}H NMR (400 MHz, DMSO-d6) d 9.01 (d, 1H, J = 4.8 Hz), 8.99 (s, 1H), 8.82 (d, 1H, J = 8.0 Hz), 8.52 (s br, 1H), 8.23 (d, 1H, J = 8.4 Hz), 8.07 (m, 3H), 7.43 (m, 1H), 7.22 (m, 2H), 7.07 (m, 2H), 5.25 (dd, 1H, J = 8.0, 2.4 Hz), 4.07 (m, 1H), 3.74 (q, 1H, J = 8.0 Hz), 2.47 (m, 1H), 2.08 (m, 2H),

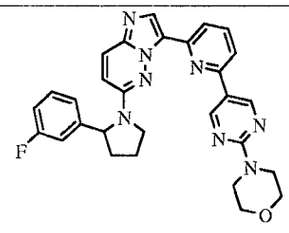
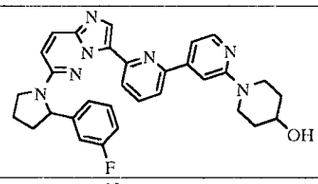
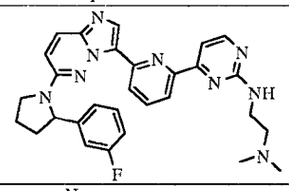
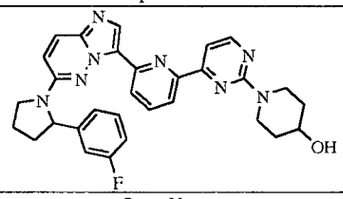
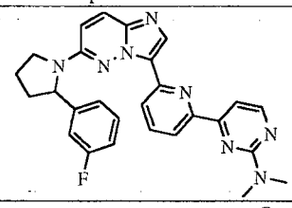
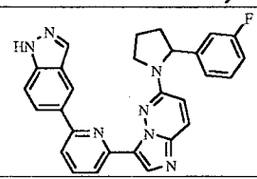
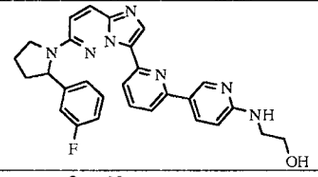
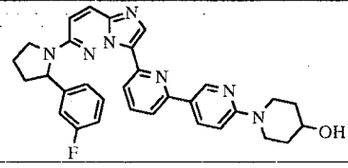
		1.92 (m, 1H) MS (m/z): 501.52
31		MS (m/z): 451.50
32		^{1}H NMR (400 MHz, DMSO-d6) d 8.42 (d, 1H, J = 4.8 Hz), 8.26 (s br, 1H), 8.31 (s, 1H), 8.15 (d, 1H, J = 8.0 Hz), 7.95 (d, 1H, J = 8.0 Hz), 7.89 (m, 1H), 7.64 (d, 1H, J = 4.8 Hz), 7.41 (ddd, 1H, J = 8.0, 6.4, 6.4 Hz), 7.20 (m, 2H), 7.05 (ddd, 1H, J = 8.4, 8.4, 2.4 Hz), 6.90 (s br, 1H), 6.76 (s, 2H), 5.22 (dd, 1H, J = 8.4, 2.8 Hz), 4.03 (m, 1H), 3.70 (q, 1H, J = 8.4 Hz), 2.47 (m, 1H), 2.06 (m, 2H), 1.89 (m, 1H) MS (m/z): 452.49
33		MS (m/z): 471.57
34		MS (m/z): 471.57
35		MS (m/z): 453.47

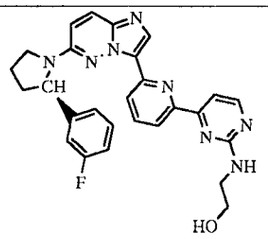
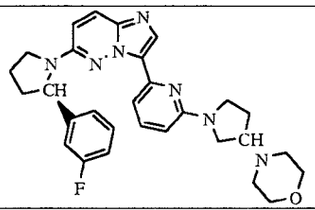
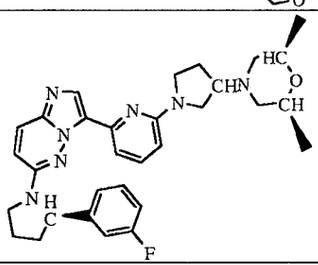
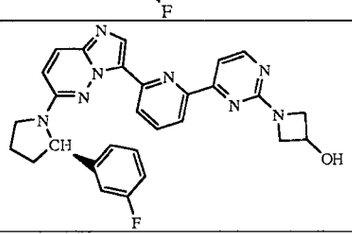
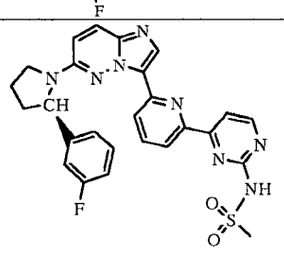
36		MS (m/z): 521.59
37		MS (m/z): 521.59
38		MS (m/z): 508.59
39		^{1}H NMR (400 MHz, DMSO-d6) 8.64 (d, 1H, J = 4.8 Hz), 8.40 (s, 1H), 8.35 (s br, 1H), 8.34 (d, 1H, J = 8.0 Hz), 8.01 (d, 1H, J = 10.0 Hz), 7.96 (m, 1H), 7.81 (d, 1H, J = 4.8 Hz), 7.46 (m, 1H), 7.26 (d, 1H, J = 7.6 Hz), 7.10 (m, 1H), 6.96 (s br, 1H), 5.27 (dd, 1H, J = 8.0, 2.8 Hz), 4.09 (m, 1H), 3.89 (t, 4H, J = 4.8 Hz), 3.78 (m, 5H), 2.53 (m, 1H), 2.12 (m, 2H), 1.95 (m, 1H) MS (m/z): 522.58
40		MS (m/z): 549.66
41		MS (m/z): 496.54

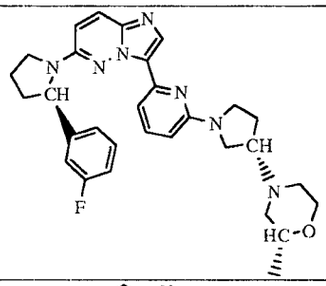
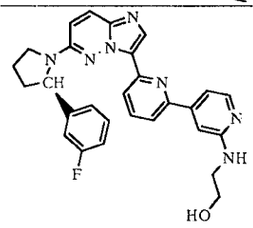
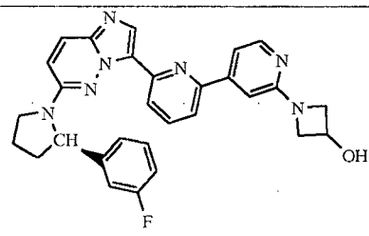
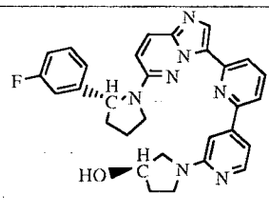
42		MS (m/z): 520.60
43		MS (m/z): 514.64
44		^{1}H NMR (400 MHz, DMSO-d6) 9.38 (d, 1H, J = 1.2 Hz), 9.05 (d, 1H, J = 5.2 Hz), 8.64 (dd, 1H, J = 9.2, 1.2 Hz), 8.46 (s, 1H), 8.36 (d, 1H, J = 8.0 Hz), 8.01 (d, 1H, J = 10.0 Hz), 7.96 (m, 1H), 7.47 (ddd, 1H, J = 8.0, 6.4, 6.4 Hz), 7.26 (m, 3H), 7.11 (ddd, 1H, J = 8.4, 8.4, 2.4 Hz), 6.98 (s br, 1H), 5.27 (dd, 1H, J = 8.0, 2.4 Hz), 4.09 (m, 1H), 3.76 (t, 4H, J = 9.2 Hz), 2.53 (m, 1H), 2.12 (m, 2H), 1.95 (m, 1H) MS (m/z): 437.47
45		MS (m/z): 513.61
46		MS (m/z): 547.65
47		MS (m/z): 501.55
48		^{1}H NMR (400 MHz, DMSO-d6) d 8.10 (s, 1H), 7.89 (d, 1H, J = 6.0 Hz), 7.54 (m, 2H), 7.39 (m, 1H), 7.17 (m, 2H), 7.04 (m, 1H), 6.81 (m, 2H), 6.40 (s, 1H), 5.18 (dd, 1H, J = 8.0, 2.4 Hz), 4.00 (m,

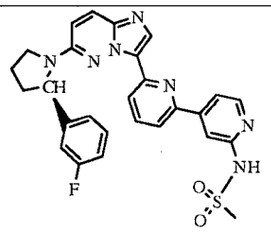
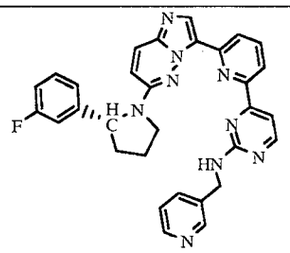
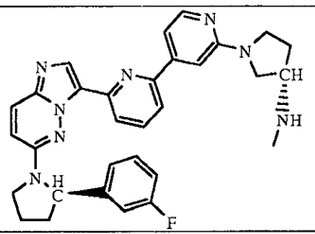
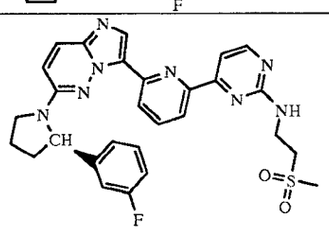
		1H), 3.69 (m, 9H), 2.45 (m, 2H), 1.87 (m, 1H), 0.96 (m, 2H), 0.80 (m, 2H) MS (m/z): 527.59
49		MS (m/z): 451.50
50		^{1}H NMR (400 MHz, DMSO-d6) d 8.09 (s, 1H), 7.90 (d, 1H, J = 10.0 Hz), 7.53 (m, 2H), 7.38 (m, 1H), 7.16 (m, 2H), 7.03 (m, 1h), 6.82 (s br, 1H), 6.77 (d, 1H, J = 8.4 Hz), 5.17 (dd, 1H, J = 8.4, 2.8 Hz), 4.00 (m, 1H), 3.86 (m, 2H), 3.59 (m, 8H), 3.40 (m, 3H), 2.94 (m, 1H), 2.45 (m, 1H), 2.04 (m, 2H), 1.87 (m, 1H), 1.58 (m, 4H) MS (m/z): 555.65
51		^{1}H NMR (400 MHz, DMSO-d6) d 8.15 9s, 1H), 7.95 (d, 1H, J = 9.6 Hz), 7.65 (d, 2H), 7.44 (d, 1H), 7.22 (m, 2H), 7.09 (m, 1H), 6.84 (m, 2H), 5.23 (dd, 1H, J = 8.0, 2.4 Hz), 4.78 (dd, 1H, J = 8.0, 5.6 Hz), 4.05 (m, 1H), 3.70 (m, 11H), 2.50 (m, 1H), 2.09 (m, 4H), 1.91 (m, 3H) MS (m/z): 541.62
52		MS (m/z): 521.59
53		MS (m/z): 506.58

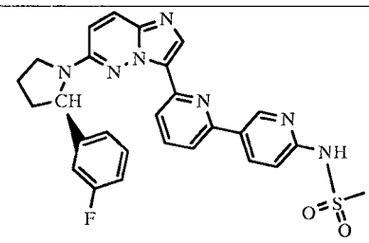
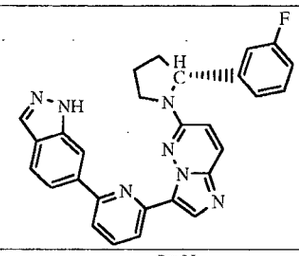
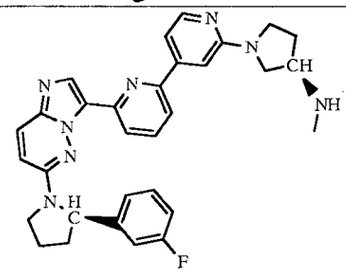
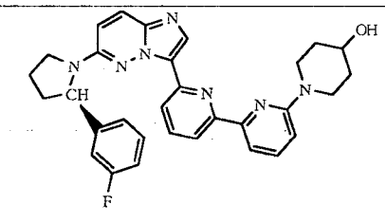
95

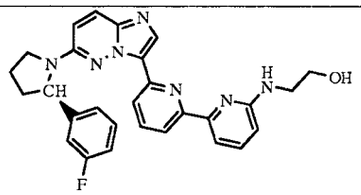
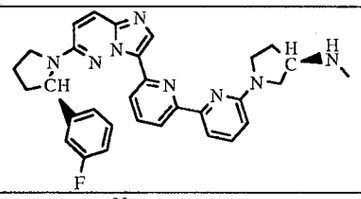
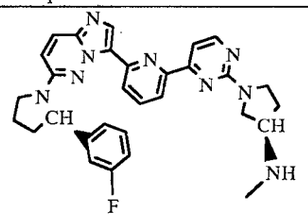
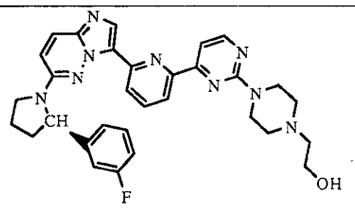
54		^{1}H NMR (400 MHz, DMSO-d6) d 9.17 (s, 1H), 8.31 (s, 1H), 8.11 (s br, 1H), 7.94 9d, 1H, J = 10.0 Hz), 7.78 (m, 2H), 7.41 (m, 2H), 7.20 (m, 2H), 7.05 (m, 1H), 6.88 (m, 1H), 5.21(dd, 1H, J = 8.0, 2.4 Hz), 4.00 (m, 1H), 3.80 (m, 4H), 3.69 (m, 5H), 2.57 (m, 1H), 2.06 (m, 2H), 1.89 (m, 1H) MS (m/z): 522.58
55		MS (m/z): 536.61
56		MS (m/z): 523.61
57		MS (m/z): 536.60
58		MS (m/z): 480.54
59		MS (m/z): 475.52
60		MS (m/z): 495.55
61		MS (m/z): 535.61

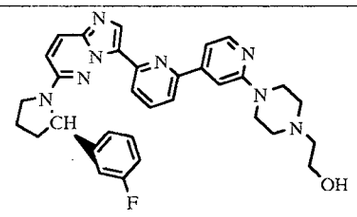
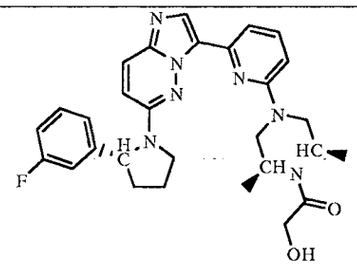
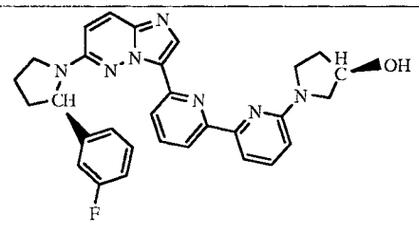
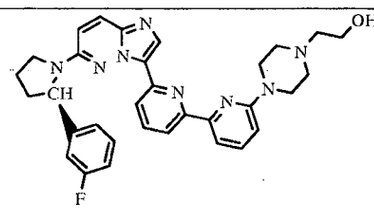
62		^{1}H NMR (400 MHz, DMSO-d6) d 8.46 (d, 1H, J = 4.8 Hz), 8.32 (s, 1H), 8.22 (s br, 1H), 7.95 (d, 1H, J = 6.0 Hz), 7.89 (m, 1H), 7.65 (d, 1H, J = 4.2 Hz), 7.42 (m ,1H), 7.19 (m, 3H), 7.05 (ddd, 1H, J = 8.0, 8.0, 2.0 Hz), 6.90 (m, 1H), 5.20 (m, 1H), 4.74 (t, 1H, J = 5.6 Hz), 4.03 (m, 1H), 3.70 (q, 1H, J = 8.4 Hz), 3.60 (m, 2H), 3.47 (s br, 2H), 3.34 (s, 1H), 2.49 (m, 1H), 2.06 (m, 2H), 1.95 (m, 1H) MS (m/z): 496.54
63		MS (m/z): 513.61
64		MS (m/z): 541.66
65		MS (m/z): 508.55
66		^{1}H NMR (400 MHz, DMSO-d6) d 8.53 (d, 1H, J = 4.4 Hz), 8.22 (s, 1H), 8.16 (s br, 1H), 8.07 (d, 1H, J = 7.6 Hz), 7.82 (m, 3H), 7.29 (m, 1H), 7.07 (m, 2H), 6.91(ddd, 1H, J = 8.4, 8.4, 2.4 Hz), 6.77 (s br, 1H), 5.08 (d, 1H, J = 8.0, Hz), 3.90 (m, 1H), 3.57 (q, 1H, J = 8.0 Hz), 3.15 (s, 3H), 3.10 (m, 1H), 2.33 (m, 1H), 1.92 (m, 2H), 1.76 (m, 1H) MS (m/z): 530.58

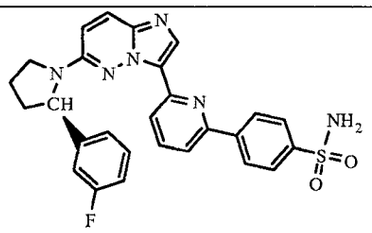
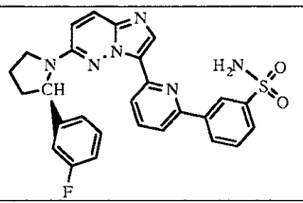
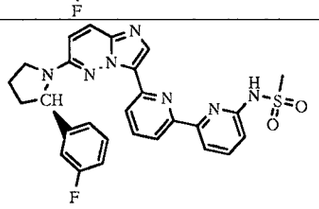
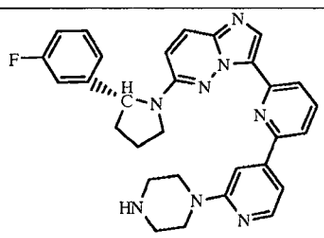
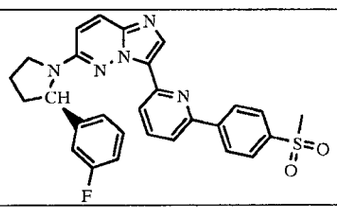
67		MS (m/z): 527.64
68		^{1}H NMR (400 MHz, DMSO-d6) d 8.31 (s, 1H), 8.18 (s br, 1H), 8.08 (d, 1H, J = 5.2 Hz), 7.95 (d, 1H, J = 9.6 Hz), 7.79 (m, 2H), 7.40 (m ,2H), 7.19 (m, 3H), 7.05 (m, 1H), 6.90 (m, 1H), 6.68 (t, 1H, J = 5.6 Hz), 5.21 (dd, 1H, J = 8.4, 2.4 Hz), 4.78 (t, 1H, J = 5.2 Hz), 4.03 (m, 1H), 3.69 (q, 1H, J = 8.4 Hz), 3.58 (m, 2H), 3.39 (q, 1H, J = 6.0 Hz), 3.34 (s, 1H), 2.46 (m, 1H), 2.05 (m, 2H), 1.89 (m, 1H) MS (m/z): 495.55
69		^{1}H NMR (400 MHz, DMSO-d6) d 8.29 (s, 1H), 8.19 (d, 1H, J = 5.2 Hz), 7.96 (d, 1H, J = 9.6 Hz), 7.91 (d, 1H, J = 8.0 Hz), 7.83 (m, 1H), 7.40 (m ,2H), 7.20 (d, 2H, J = 7.6 Hz), 7.09 (s, 1H), 7.05 (m, 1H), 6.90 (s br, 1H), 5.67(d, 1H, J = 6.8 Hz), 5.20 (dd, 1H, J = 8.0, 2.4 Hz), 4.61 (m, 1H), 4.25 (t, 1H, J = 8.0 Hz), 4.03 (m, 1H), 3.76 (q, 1H, J = 4.0Hz), 3.70 (m, 1H), 3.34 (s, 4H), 2.49 (m, 1H), 2.06 (m, 2H), 1.89 (m, 1H) MS (m/z): 507.56
70		^{1}H NMR (400 MHz, DMSO-d6) d 8.28 (s, 1H), 8.24 (s br, 1H), 8.18 (d, 1H, J = 5.2 Hz), 7.95 (d, 1H, J = 9.6 Hz), 7.90 (d, 1H, J = 8.0 Hz), 7.82 (m, 1H), 7.40 (q, 1H, J = 8.4 Hz), 7.27 (m, 1Hz), 7.19 (d, 1H, J = 7.6 Hz) 7.14 (s, 1H), 7.05 (m, 1H), 6.89 (s br, 1H), 5.19 (dd, 1H, J = 8.0, 2.4 Hz), 4.99 (d, 1H, J = 3.2 Hz), 4.43 (s, 1H), 4.02 (m, 1H), 3.90 (q, 1H, J = 9.2Hz), 3.58 (m, 1H), 3.42 (d, 1H, J = 10.8 Hz), 2.46 (m, 1H), 2.05 (m, 3H), 1.91 (m,

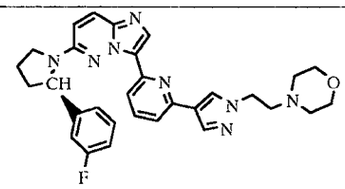
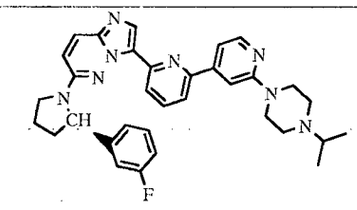
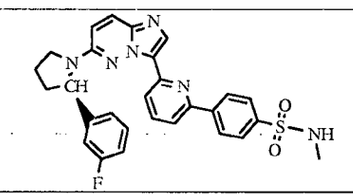
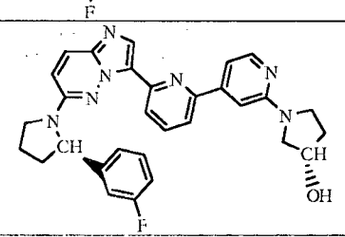
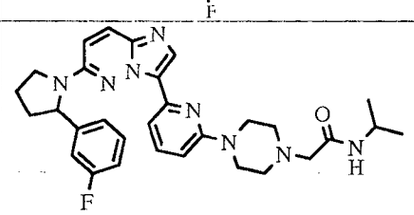
		2H) MS (m/z): 521.59
71		^{1}H NMR (400 MHz, DMSO-d6) d 8.31 (d, 1H, J = 5.6 Hz), 8.29 (s, 1H), 8.25 (s br, 1H), 7.96 (d, 1H, J = 10.0 Hz), 7.87 (m, 2H), 7.73 (s, 1H), 7.60 (dd, 1H, J = 5.6, 1.2 Hz), 7.41(m, 1H), 7.20 (d, 1H, J = 8.4 Hz), 7.05 (m, 1H), 6.91 (s br, 1H), 5.21(dd, 1H, J = 8.4, 2.4 Hz), 4.03 (m, 1H), 3.71 (q, 1H, J = 8.0 Hz), 3.23 (s, 3H), 3.20 (m, 1H), 2.47 (m, 1H), 2.06 (m, 2H), 1.89 (m, 1H) MS (m/z): 529.59
72		^{1}H NMR (400 MHz, DMSO-d6) d 8.65 (s br, 1H), 8.48(d, 1H, J = 5.2 Hz), 8.44 (dd, 1H, J = 4.8, 1.6 Hz), 8.31 (s, 1H), 8.18 (d, 1H, J = 8.0 Hz), 7.95 (d, 2H, 9.6 Hz), 7.88 (m, 1H), 7.81 (m, 1H), 7.68 (d, 1H, J = 6.8 Hz), 7.39 (m, 2H), 7.19 (m, 2H), 7.05(ddd, 1H, J = 8.0, 8.0, 2.0 Hz), 6.90 (s br, 1H), 5.21 (dd, 1H, J = 6.0, 1.6Hz), 4.63 (d, 2H, J = 5.6Hz), 4.03 (m 1H), 3.70 (q, 1H, J = 8.4 Hz), 3.34 (s, 1H), 2.46 (m, 1H), 2.05 (m, 2H), 1.88 (m, 1H) MS (m/z): 543.60
73		MS (m/z): 534.63
74		^{1}H NMR (400 MHz, DMSO-d6) d 8.51 (d, 1H, J = 4.8 Hz), 8.33 (s, 1H), 8.26 (s br, 1H), 7.96 (d, 1H, J = 9.6 Hz), 7.90 (m, 1H), 7.73 (d, 1H, J = 4.8 Hz), 7.45(m, 2H), 7.20 (m, 2H), 7.05(ddd, 1H, J = 8.4, 8.4, 2.0 Hz), 6.91 (s br, 1H), 5.21 (dd, 1H, J = 8.0, 2.8 Hz), 4.04 (m, 1H),3.81 (m, 2H), 3.71 (q, 1H, J = 8.0 Hz), 3.45 (t, 2H, J = 6.8 Hz), 3.34 (s, 1H), 3.07(s, 3H), 2.46 (m, 1H), 2.06 (m, 2H),

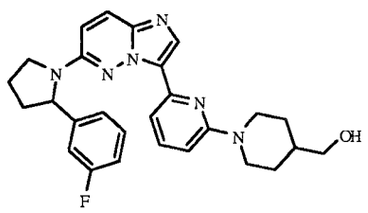
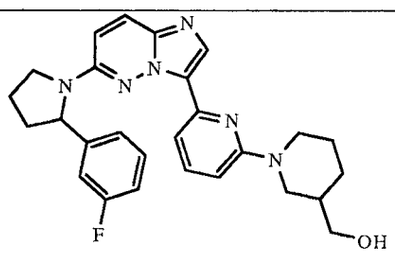
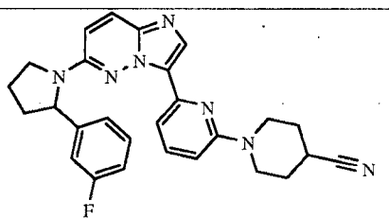
		1.89 (m, 1H) MS (m/z): 558.63
75		^{1}H NMR (400 MHz, DMSO-d6) d 8.98 (d, 1H, J = 6.0 Hz), 8.45 (dd, 1H, J= 8.8, 2.0 Hz), 8.31 (s, 1H), 8.10 (s br, 1H), 7.95 (d, 1H, J = 10.0 Hz), 7.80 (m, 2H), 7.41 (m, 1H), 7.07 (m, 2H), 6.91(ddd, 1H, J = 8.4, 8.4, 2.4 Hz), 6.77 (s br, 1H), 5.08 (dd, 1H, J = 8.0, 2.4 Hz), 3.90 (m, 1H), 3.57 (q, 1H, J = 8.0 Hz), 3.15 (s, 3H), 3.10 (m, 1H), 2.33 (m, 1H), 1.92 (m, 2H), 1.76 (m, 1H) MS (m/z): 529.59
76		MS (m/z): 475.52
77		^{1}H NMR (400 MHz, DMSO-d6) d 8.30 (s, 1H), 8.23 (d, 1H, J = 5.6 Hz), 8.1 (s br, 1H), 7.95 (t, 2H, J = 8.8 Hz), 7.85 (s br, 1H), 7.39 (m, 2H), 7.21 (m, 3H), 7.05 (m, 1H), 6.90(s br, 1H), 5.21 (dd, 1H, J = 8.0, 2.8 Hz), 4.03 (m, 1H), 3.80 (m, 2H), 3.67 (m, 3H), 2.61 (s, 3H), 2.47 (m, 1H), 2.35 (m, 1H), 2.20 (m, 1H), 2.06 (m, 2H), 1.89 (m, 1H), 1.18 (d, 1H, J = 6.8 Hz) MS (m/z): 534.63
78		^{1}H NMR (400 MHz, DMSO-d6) δ 8.29 (s, 1H), 8.19 (d, 1H, J = 8.0 Hz), 7.94 (d, 1H, J = 9.6 Hz), 7.84 (m, 3H), 7.68 (t, 2H, J = 8.4 Hz), 7.41 (m, 1H), 7.19 (m, 2H), 7.05 (m, 1H), 6.93 (d, 1H, J = 8.4 Hz), 6.90(s br), 5.21 (dd, 1H, J = 8.0, 2.8 Hz), 4.73 9d, 1H, J = 4.4 Hz), 4.16 (m ,2H), 4.03 (m, 1H), 3.73 (m, 2H), 3.17 (m, 2H), 2.47 (m, 1H), 2.06 (m, 2H), 1.87 (m, 3H), 1.44 (m, 2H) MS (m/z): 535.61

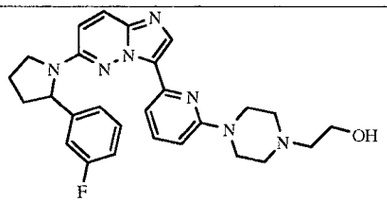
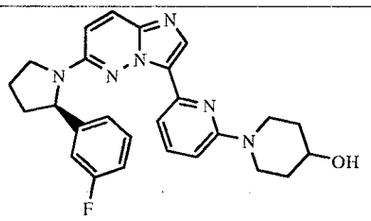
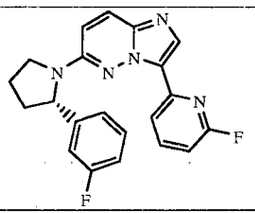
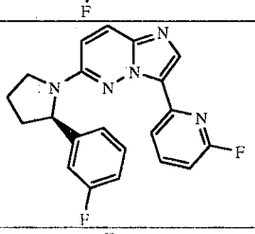
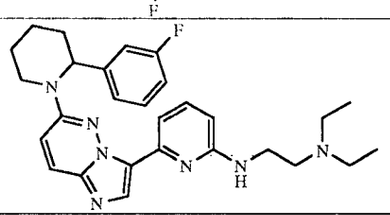
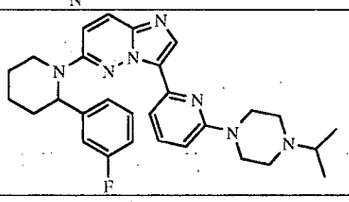
79		^{1}H NMR (400 MHz, DMSO-d6) δ 8.28 (s, 1H), 8.14 (d, 1H, J = 8.0 Hz), 7.94 (d, 1H, 9.6 Hz), 7.82 (m, 1H), 7.68 (d, 1H, J = 7.2 Hz), 7.53 (t, 1H, J = 7.2 Hz), 7.41 (ddd, 1H, J = 8.0, 8.0, 6.4 Hz)), 7.19 (m, 2H), 7.05 (ddd, 1H, J = 8.4, 8.4, 2.0 Hz), 6.88(s br, 1H), 6.665 (t, 1H, J = 5.6 Hz), 6.58 (d, 1H, J = 8.0 Hz), 5.21 (dd, 1H, J = 8.0, 2.4 Hz), 4.79 (t, 1H, J = 5.6 Hz), 4.03 (m, 1H), 3.66(m, 3H), 3.46 (m, 2H), 2.45 (m, 1H), 2.06 (m, 2H), 1.89 (m, 1H) MS (m/z): 495.55
80		MS (m/z): 534.63
81		^{1}H NMR (400 MHz, DMSO-d6) δ 8.57 (s, 1H,J = 5.2 Hz), 8.39 (s, 1H), 8.36 (s br, 1H), 8.34(d, 1H, J = 7.6 Hz), 7.99 (m, 2H), 7.72 (d, 1H, J = 4.2 Hz), 7.47 (m, 1H), 7.26 (m, 2H), 7.11 (m, 1H), 6.96 (s br, 1H), 5.27 (dd, 1H, J = 8.0, 2.0 Hz), 4.09 (m, 1H), 3.58 (m, 4H), 3.49 (s br, 1H), 3.46 (m, 2H), 2.53 (m, 1H), 2.40 (s, 3H), 2.15 (m, 3H), 1.93 (m, 2H) MS (m/z): 535.62
82		^{1}H NMR (400 MHz, DMSO-d6) δ 8.54 (d, 1H, J = 4.2 Hz), 8.33 (s, 1H), 8.25 (d, 1H, J = 7.6 Hz), 8.28 (br s, 1H), 7.94 (d, 1H, J = 10. 0 Hz), 7.89 (m, 1H), 7.68 (d, 1H, J = 4.8 Hz), 7.40 (m, 1H), 7.19 (m, 2H), 7.04 (m, 1H), 6.88 (br s, 1H), 5.20 (dd, 1H, J = 8.0, 2.8 Hz), 4.48 (br s, 1H), 4.02 (m, 1H), 3.85 (m, 4H), 3.69 (1, 1H, J = 9.2 Hz), 3.57 (t, 2H, J = 6.0 Hz), 2.50 (m, 7H), 2.05 (m, 2H), 1.89 (m, 1H) MS (m/z): 565.64

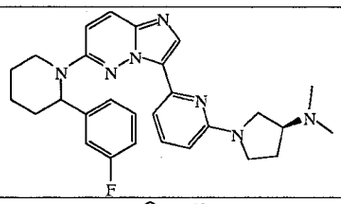
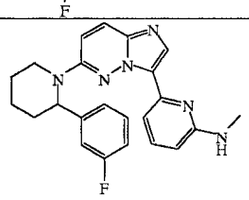
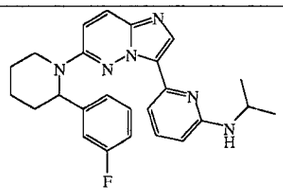
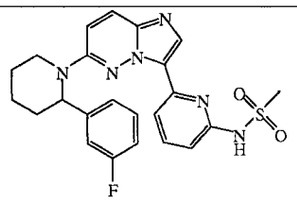
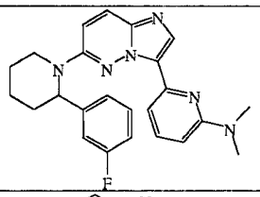
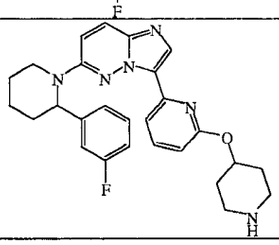
83		^{1}H NMR (400 MHz, DMSO-d6) δ 8.38 (s, 1H), 8.30 (d, 1H, J = 4.2 Hz), 8.01 (m, 2H), 7.98 (br s, 1H), 7.89(m, 1H), 7.59 (s, 1H), 7.46 (m, 2H), 7.26 (d, 2H, J = 7.6 Hz), 7.11 (m, 1H), 6.69 (br s, 1H), 5.27 (dd, 1H, J = 8.4, 2.4 Hz), 4.53 (m, 1H), 4.021(m, 1H), 3.76 (m, 1H), 3.64 (m, 6H), 2.61 (t, 4H, 4.8 Hz), 2.53 (m, 3H), 2.11 (m, 2H), 1.96 (m, 1H) MS (m/z): 564.66
84		MS (m/z): 529.61
85		^{1}H NMR (400 MHz, DMSO-d6) δ 8.29 (s, 1H), 8.23 (d, 1H, J = 7.6 Hz), 8.15 (br s, 1H), 7.93 (d, 1H, J = 10.0 Hz), 7.82 (m, 1H),), 7.76 (d, 1H, J = 7.2 Hz), 7.65 (t, 1H, J = 8.0 Hz), 7.40 (ddd, 1H, J = 8.0, 8.0, 6.4 Hz), 7.18 (m, 2H), 7.04 (ddd, 1H, J = 8.8, 8.0, 2.4 Hz), 6.86 (br s, 1H), 6.52 (d, 1H, J = 8.0 Hz), 5.19 (dd, 1H, J = 8.4, 2.4 Hz), 5.00 (s br, 1H), 4.44 (m, 1H), 4.02 (m, 1H), 3.69 (q, 1H, J = 7.6 Hz), 3.58 (m, 3H), 3.37 (m, 1H), 2.48 (m, 3H), 1.96 (m, 2H) MS (m/z): 521.56
86		^{1}H NMR (400 MHz, DMSO-d6) δ 8.35 (s, 1H), 8.25 (d, 1H, J = 48.0 Hz), 8.20 (s br, 1H), 7.90 (d, 1H, J = 8.0 Hz), 7.81 (br s, 1H), 7.76 (t, 1H, J = 8.0 Hz), 7.46 (q, 1H, J = 8.0 Hz), 7.25 (m, 2H), 7.11 (m, 1H), 6.97 (d, 1H, J = 8.4 Hz), 6.92 (br s, 1H), 5.26 (d, 1H, J = 8.0 Hz), 4.54 (m, 1H), 4.08 (m, 1H), 3.67 (m, 7H), 2.63 (t, 4H, J = 4.2 Hz), 2.52 (t, 3H, J = 6.4 Hz), 2.11 (m, 2H), 1.96 (m, 1H)

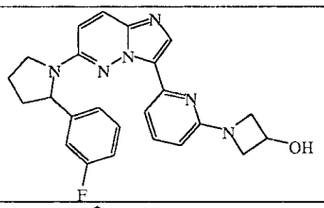
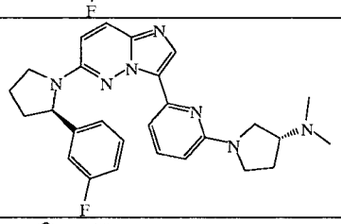
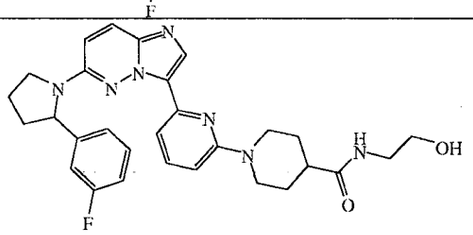
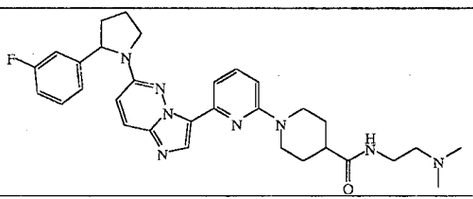
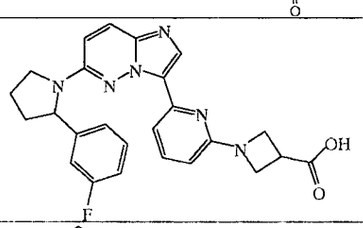
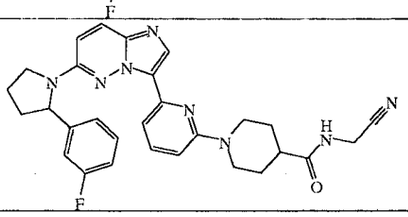
		MS (m/z): 564.66
87		^{1}H NMR (400 MHz, DMSO-d6) δ 8.44 (d, 1H, 8.0 Hz), 8.40 (s, 1H), 8.00(m, 3H), 7.91 (s br, 1H), 7.76 (m, 1H), 7.52 (s, 2H), 7.46 (m, 1H), 7.27 (d, 2H, J = 7.6 Hz), 7.11 (m, 1H), 6.97 (s br, 1H), 5.28 (dd, 1H, J = 8.4, 2.4 Hz), 4.20 (dd, 1H, J = 6.0, 3.2 Hz), 4.10 (m, 1H), 3.77 (1, 1H, J = 8.0 Hz), 2.60 (s, 1H), 2.53 (m, 1H), 2.12 (m, 2H), 1.95 (m, 1H) MS (m/z): 514.57
88		MS (m/z): 514.57
89		^{1}H NMR (400 MHz, DMSO-d6) δ 8.40 (s, 1H), 8.23 (d, 1H, ϑ = 7. 6 Hz), 8.19 (d, 1H, J = 7.6 Hz), 8.10 (d, 1H, J = 8.0 Hz), 7.95 (m, 2H), 7.48 (ddd, 1H, J = 8.0, 6.4, 6.4 Hz), 7.25 (m, 3H), 7.10 (ddd, 1H, J = 8.8, 8.8, 2.4 Hz), 7.03 (d, 1H, J = 8.0 Hz), 6.95 (s br, 1H), 5.26 (dd, 1H, J = 8.4, 2.4 Hz), 4.09 (m, 1H), 3.75 (q, 1H, J = 8.4 z), 3.51 (s, 3H), 2.55 (m, 1H), 2.11 (m, 2H), 1.91 (m, 1H) MS (m/z): 529.59
90		MS (m/z): 520.60
91		MS (m/z): 513.59

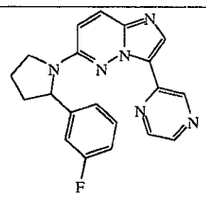
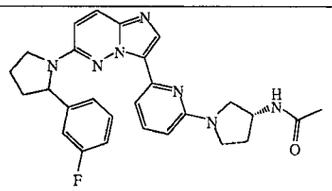
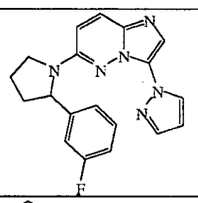
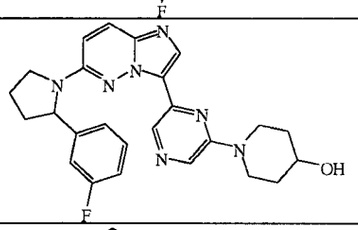
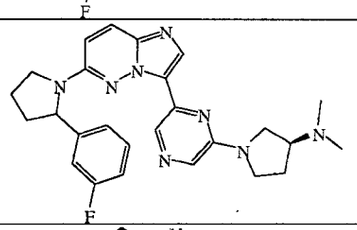
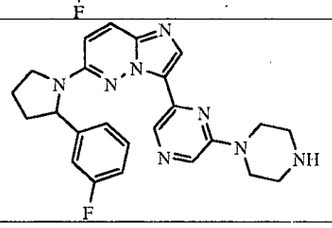
92		^{1}H NMR (400 MHz, DMSO-d6) δ 8.49 (s, 1H), 8.33 (s, 1H), 8.14 (s, 1H), 8.05 (s br, 1H), 7.99 (d, 1H, J = 9.6 Hz), 7.77 (m, 1H), 7.56 (d, 1H, J = 7.6 Hz), 7.45 (m, 1H), 7.24 (m, 2H), 7.10 (m, 1H), 6.95 (s br, 1H), 5.26 (dd, 1H, J = 8.0, 2.8 Hz), 4.34 (t, 2H, J = 7.2 Hz), 4.08 (m, 1H), 3.75 (q, 1H, J = 8.4 z), 3.62 (t, 4H, J = 4.2 Hz), 2.83 (t, 2H, J = 6.8 Hz), 2.55 (m, 4H), 2.11 (m, 2H), 1.91 (m, 1H) MS (m/z): 538.62
93		^{1}H NMR (400 MHz, DMSO-d6) δ 8.38 (s, 1H), 8.29 (d, 1H, J = 4.2 Hz), 8.20 (s br, 1H), 8.01 (m, 2H), 7.90 (m, 1H), 7.59 (s, 1H), 7.46 (m, 2H), 7.26 (d, 2H, J = 7.6 Hz), 7.11 (m, 1H), 6.96 (s br, 1H), 5.27 (dd, 1H, J = 8.0, 2.8 Hz), 4.09 (m, 1H), 3.76 (m, 1H), 3.64 (m, 3H), 3.40 (s, 2H), 2.76 (m, 1H), 2.64 (m, 3H), 2.53 (m, 1H), 2.12 (m, 2H), 1.95 (m, 1H), 1.08 (d, 6H, J = 6.4 Hz) MS (m/z): 562.68
94		MS (m/z): 528.60
95		MS (m/z): 521.59
96		1H NMR (DMSO-d6) 8.07 (s, 1 H), 7.88 (d, 1 H), 7.50-7.58 (bs, 1 H), 7.42-7.48 (bs, 1 H), 7.35-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.01-7.05 (m, 1 H), 6.78-6.85 (bs, 1 H), 6.73 (d, 1H), 5.15-5.18 (q, 1 H), 3.96-4.01 (m, 1 H), 3.87-3.94 (m, 1 H), 3.64-3.70 (m, 1 H), 3.54-360 (bs, 4 H), 2.91-2.96 (bs, 2 H), 2.50-2.60 (bs, 4 H), 2.45-2.50 (m, 1 H), 2.00-2.06 (m, 2 H),

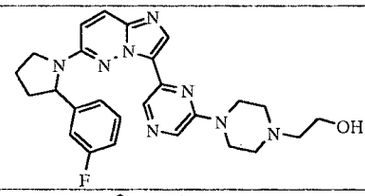
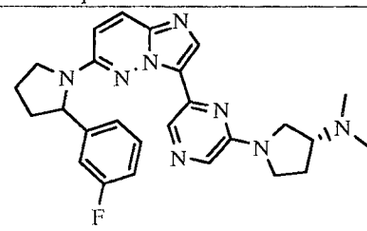
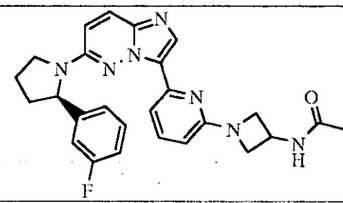
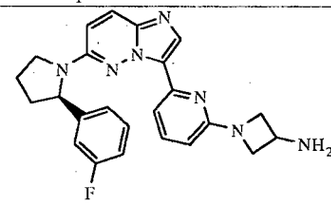
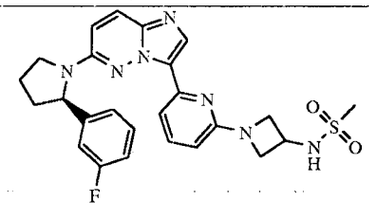
		1.84-1.90 (m, 1 H), 1.08 (d, 6 H). MS (m/z): 543.7
97		1H NMR (DMSO-d6) 8.04 (s, 1 H), 7.87 (d, 1 H), 7.40-7.50 (m, 2 H), 7.35-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.01-7.05 (m, 1 H), 6.76-6.85 (bs, 1H), 6.72 (d, 1H), 5.14-5.17 (q, 1 H), 4.46 (t, 1 H), 4.37 (d, 2 H), 3.96-4.01 (m, 1 H), 3.64-3.69 (q, 1 H), 3.27 (t, 2 H), 2.74-2.81 (m, 2 H), 2.45-2.50 (m, 1 H), 2.00-2.06 (m, 2 H), 1.84-1.89 (m, 1 H), 1.58-1.64 (m, 1 H), 1.08-1.17 (m, 2 H). MS (m/z): 473.6
98		1H NMR (DMSO-d6) 8.05 (s, 1 H), 7.88 (d, 1 H), 7.40-7.50 (m, 2 H), 7.34-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.00-7.05 (m, 1 H), 6.76-6.85 (bs, 1H), 6.69 (t, 1 H), 5.15-5.18 (q, 1 H), 4.54-4.57 (m, 1 H), 4.34 (d, 1 H), 4.22 (d, 1 H), 3.96-4.02 (m, 1 H), 3.64-3.70 (q, 1 H), 3.28-3.37 (m, 2 H), 2.81-2.88 (m, 1 H), 2.59 (t, 1 H), 2.45-2.50 (m, 1 H), 2.00-2.08 (m, 2 H), 1.84-1.90 (m, 1 H), 1.72-1.77 (m, 1 H), 1.66-1.72 (m, 1 H), 1.58-1.65 (m, 1 H), 1.40-1.59 (m, 1 H), 1.14-1.22 (m, 1 H). MS (m/z): 473.6
99		1H NMR (DMSO-d6) 8.07 (s, 1 H), 7.88 (d, 1 H), 7.41-7.60 (m, 2 H), 7.34-7.40 (m, 1 H), 7.12-7.18 (m, 2 H), 7.00-7.15 (m, 1 H), 6.78-6.85 (bs, 1H), 6.77 (d, 1H), 5.15-5.18 (q, 1 H), 3.96-4.01 (m, 1 H), 3.83-3.89 (m, 2 H), 3.64-3.70 (q, 1 H), 3.09-3.14 (m, 1 H), 2.45-2.50 (m, 1 H), 2.00-2.06 (m, 2 H), 1.94-1.97 (m, 2 H), 1.84-1.89 (m, 1 H), 1.71-1.77 (m, 2 H). MS (m/z): 468.5

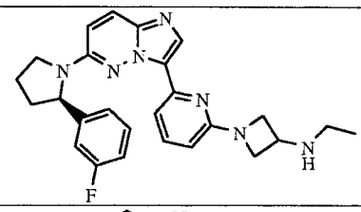
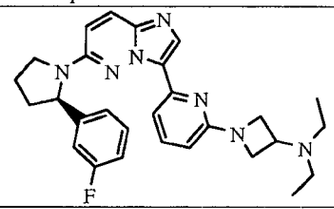
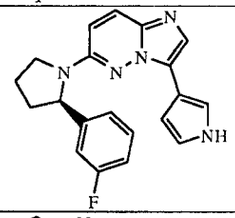
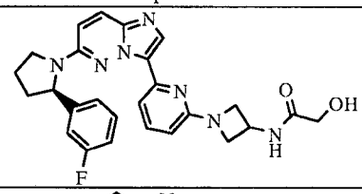
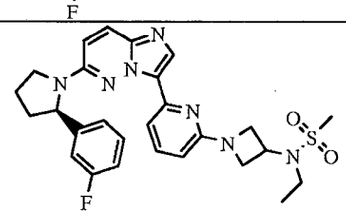
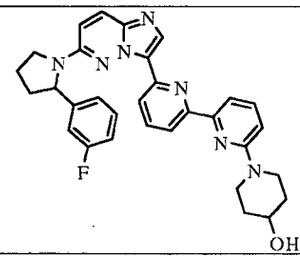
100		1H NMR (DMSO-d6) 8.05(s, 1 H), 7.88 (d, 1 H), 7.42-7.60 (m, 2 H), 7.35-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.00-7.05 (m, 1 H), 6.75-6.85 (bs, 1H), 6.72 (d, 1H), 5.14-5.18 (q, 1 H), 4.43 (t, 1 H), 3.96-4.01 (m, 1 H), 3.63-3.70 (q, 1 H), 3.47-3.57 (m, 6 H), 2.50-2.55 (m, 4 H), 2.40-2.50 (m, 3 H), 2.00-2.06 (m, 2 H), 1.84-1.89 (m, 1 H). MS (m/z): 488.6
101		1H NMR (CDCl3-d6) d 8.24 (s, 1 H), 7.69 (d, 1 H, J=9.6 Hz), 7.55-7.63 (m, 1 H), 7.43 (t, 1 H), 7.25-7.33 (m, 1 H), 7.05 (d, 1 H, J=7.6 Hz), 6.90-7.00 (m, 2 H), 6..59 (d, 1 H, J=8.4 Hz), 6.51 (d, 1 H, j=9.6 Hz), 5.04-5.11 (m, 1 H), 4.13-4.22 (m, 2 H), 3.90-4.00 (m, 2 H) , 3.69-3.78 (m, 1 H), 3.13-3.22 (m, 2H), 2.42-2.54 (m, 1 H), 2.06-2.20 (m, 2 H), 1.96-2.05 (m, 3 H), 1.55-1.62 (m, 2 H) MS (m/z): 459.5
102		MS (m/z): 378.4
103		MS (m/z): 378.4
104		MS (m/z): 488.6
105		MS (m/z): 500.6

106		MS (m/z): 486.6
107		1H NMR (DMSO-d6): d 8.06 (s, 1 H), 7.75 (s, 1 H), 7.51 (d, 1 H), 7.32-7.40 (m, 2 H), 7.22 (d, 1 H), 7.14 (d, 2 H), 6.99-7.05 (m, 1 H), 6.45-6.50 (m, 1 H), 6.35 9d, 1 H), 4.14-4.21 (m, 1 H), 3.30-3.39 (m, 2 H), 2.82 (d, 3 H), 2.17-2.26 (m, 1 H), 2.00-2.10 (m, 1 H), 1.56-1.83 (m, 3 H), 1.35-1.50 (m, 1 H). MS (m/z): 403.5
108		1H NMR (DMSO-d6): d 8.02 (s, 1 H), 7.90 (d, 1 H), 7.46 (d, 1 H), 7.30-7.40 (m, 2 H), 7.21 (d, 1 H), 7.13 (d, 2 H), 6.98-7.06 (m, 1 H), 6.30-6.36 (m, 2 H), 4.12-4.20 (m, 1 H), 4.02-4.10 (m, 1 H), 3.30-3.38 (m, 2 H), 2.18-2.26 (m, 1 H), 2.00-2.10 (m, 1 H), 1.56-1.84 (m, 3 H), 1.36-1.48 (m, 1 H), 1.17 (d, 6 H). MS (m/z): 431.5
109		1H NMR (DMSO-d6): d 10.63 (s, 1 H), 8.06 (s, 1 H), 7.97 (s, 1 H), 7.94 (d, 1 H), 7.72 (t, 1 H), 7.33-7.40 (m, 1 H), 7.25 (d, 1 H), 7.12-7.18 (m, 2 H), 6.99-7.05 (m, 1 H), 6.80 (d, 1 H), 4.15-4.22 (m, 1 H), 3.42 (s, 3 H), 3.35-3.42 (m, 2 H), 2.17-2.26 (m, 1 H), 2.01-2.14 (m, 1 H), 1.57-1.85 (m, 3 H), 1.36-1.49 (m, 1 H). MS (m/z): 467.5
110		MS (m/z): 417.5
111		MS (m/z): 473.6

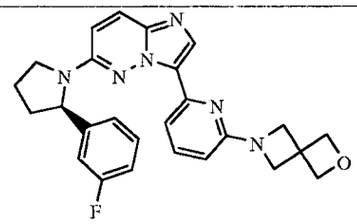
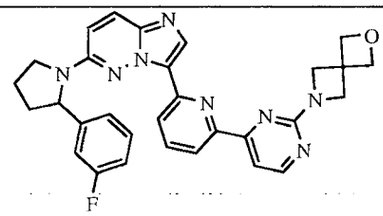
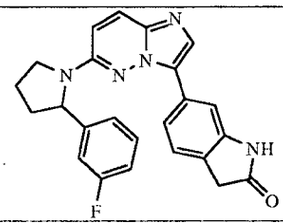
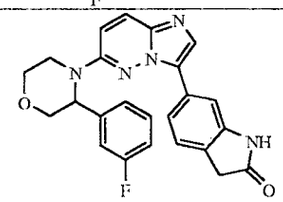
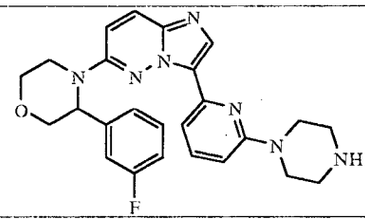
112		MS (m/z): 431.5
113		MS (m/z): 472.6
114		1H NMR (DMSO-d6) 8.05 (s, 1 H), 7.88 (d, 1 H, J=9.6 Hz), 7.81 (t, 1 H, J=5.6 Hz), 7.34-7.58 (m, 3 H), 7.10-7.18 (m, 2 H), 7.00-7.06 (m, 1H), 6.76-6.86 (bs, 1 H), 6.74 (d, 1 H, J=8.8 Hz), 5.14-5.19 (m, 1 H), 4.64 (t, 1 H, J=5.6 Hz), 4.33-4.42 (m, 2 H), 3.95-4.02 (m, 1 H), 3.62-3.71 (m, 1 H), 3.34-3.42 (m, 2 H), 3.07-3.13 (m, 2 H), 2.76-2.86 (m, 2 H), 2.44-2.50 (m, 1 H), 2.32-2.44 (m, 1 H), 2.00-2.10 (m, 2 H), 1.84-1.91 (m, 1 H), 1.67-1.78 (m, 2 H), 1.46-1.60 (m, 2 H). MS (m/z): 530.6
115		MS (m/z): 557.7
116		MS (m/z): 459.5
117		MS (m/z): 525.6

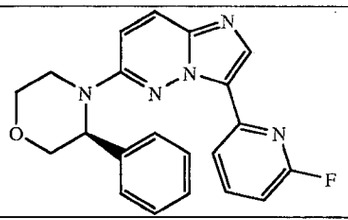
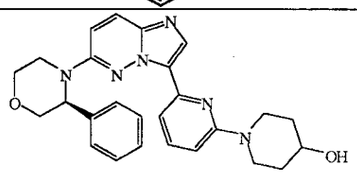
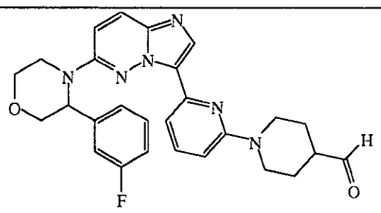
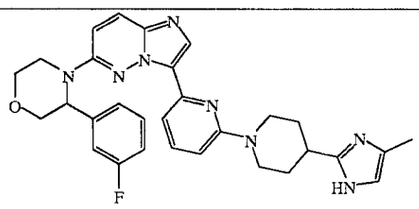
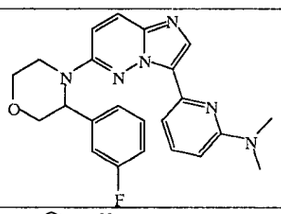
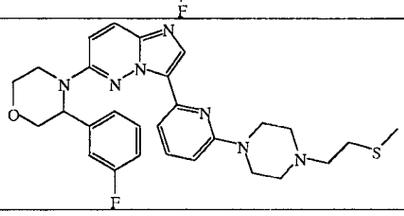
118		1H NMR (DMSO-d6) 9.30-9.60 (bs, 1 H), 8.63-8.66 (m, 1H), 8.52 (d, 1 H, J=12.4 Hz), 8.16 (s, 1 H), 7.95 (d, 1 H, J=10 Hz), 7.32-7.40 (m, 1 H), 7.11-7.17 (m, 2 H), 6.98-7.06 (m, 1H), 6.78-6.92 (bs, 1 H), 5.19-5.24 (m, 1 H), 3.98-4.05 (m, 1 H), 3.64-3.74 (m, 1 H), 2.44-2.50 (m, 1 H), 2.00-2.10 (m, 2 H), 1.85-1.93 (m, 1 H). MS (m/z): 361.4
119		1H NMR (DMSO-d6) 8.16 (d, 1 H, J=6.8 Hz), 8.04 (s, 1 H), 7.87 (d, 1 H, J=9.6 Hz), 7.44-7.60 (bs, 1 H), 7.34-7.44 (m, 2 H), 7.12-7.20 (m, 2 H), 7.00-7.06 (m, 1H), 6.72-6.90 (bs, 1H), 6.36 (d, 1 H, J=8.4 Hz), 5.14-5.20 (m, 1 H), 4.30-4.40 (m, 1 H), 3.96-4.02 (m, 1 H), 3.61-3.72 (m, 2 H), 3.42-3.60 (m, 2 H), 3.24-3.30 (m, 1 H), 2.42-2.50 (m, 1 H), 2.10-2.20 (m, 1 H), 2.00-2.10 (m, 2 H), 1.82-1.90 (m, 2 H), 1.81 (s, 3 H). MS (m/z): 486.6
120		MS (m/z): 349.4
121		MS (m/z): 460.5
122		MS (m/z): 473.6
123		MS (m/z): 445.5

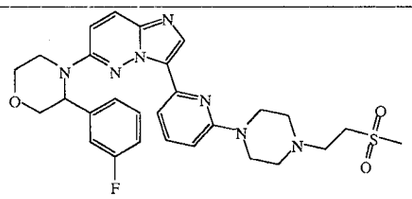
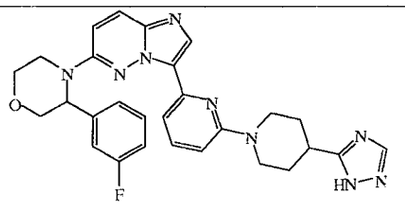
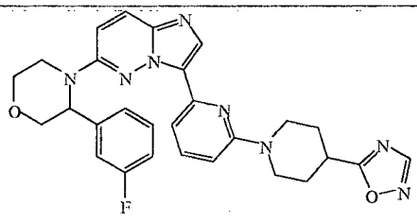
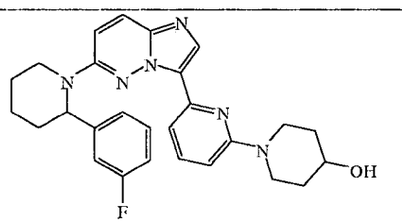
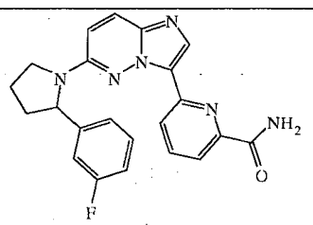
124		MS (m/z): 489.6
125		1H NMR (DMSO-d6) 8.70-8.88 (bs, 1 H), 8.12 (s, 1 H), 7.86-7.90 (m, 2 H), 7.34-7.39 (m, 1 H), 7.04-7.15 (m, 2 H), 7.00-7.06 (m, 1 H), 6.65-6.82 (m, 1H), 5.17-5.23 (m, 1 H), 3.95-4.05 (m, 1 H), 3.75-3.83 (m, 1 H), 3.64-3.74 (m, 2 H), 3.36-3.45 (m, 1 H), 3.15-3.23 (m, 1 H), 2.75-2.85 (m, 1 H), 2.42-2.50 (m, 1 H), 2.24 (s, 6 H), 2.13-2.22 (m, 1 H), 1.95-2.08 (m, 2 H), 1.75-1.92 (m, 2 H). MS (m/z): 473.6
126		MS (m/z): 472.5
127		1H NMR (DMSO-d6) 8.01 (s, 1 H), 7.88 (d, 1 H, J=10 Hz), 7.46-7.62 (bs, 1 H), 7.32-7.44 (m, 2 H), 7.12-7.18 (m, 2 H), 7.00-7.06 (m, 1H), 6.72-6.90 (bs, 1H), 6.27 (d, 1 H, J=8 Hz), 5.13-5.20 (m, 1 H), 4.09-4.16 (m, 2 H), 3.95-4.03 (m, 1 H), 3.76-3.85 (m, 1 H), 3.62-3.71 (m, 1 H), 3.51-3.57 (m, 2 H), 2.41-2.50 (m, 1 H), 2.00-2.10 (m, 2 H), 1.83-1.90 (m, 1 H). MS (m/z): 430.5
128		1H NMR (DMSO-d6) 8.03 (s, 1 H), 7.89 (d, 1 H, J=10 Hz), 7.83 (d, 1 H, J=8 Hz), 7.50-7.62 (bs, 1 H), 7.41-7.50 (m, 1 H), 7.34-7.42 (m, 1 H), 7.12-7.18 (m, 2 H), 7.00-7.06 (m, 1H), 6.78-6.90 (bs, 1H), 6.32 (d, 1 H, J=8.4 Hz), 5.04-5.20 (m, 1 H), 4.24-4.36 (m, 3 H), 3.95-4.02 (m, 1 H), 3.77-3.85 (m, 2 H), 3.60-3.71 (m, 1 H), 2.95 (s, 3 H), 2.42-2.50 (m, 1 H), 2.00-2.07 (m, 2 H), 1.82-1.90 (m, 1 H). MS (m/z): 508.6

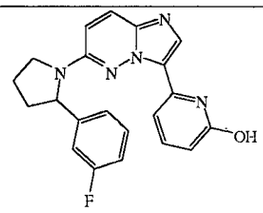
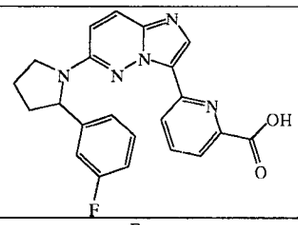
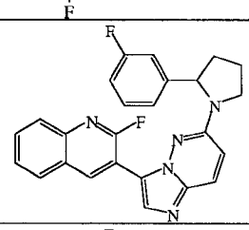
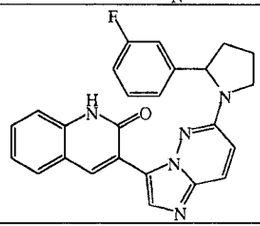
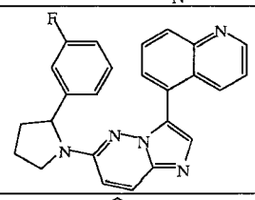
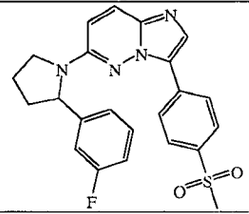
129		MS (m/z): 458.5
130		MS (m/z): 458.6
131		MS (m/z): 348.4
132		MS (m/z): 488.5
133		1H NMR (DMSO-d6) 8.03 (s, 1 H), 7.88 (d, 1 H, J=10 Hz), 7.52-7.64 (bs, 1 H), 7.42-7.50 (m, 1 H), 7.32-7.42 (m, 1 H), 7.12-7.18 (m, 2 H), 7.00-7.06 (m, 1H), 6.74-6.90 (bs, 1H), 6.34 (d, 1 H, J=8 Hz), 5.12-5.2 (m, 1 H), 4.62-4.70 (m, 1 H), 4.22-4.32 (m, 2 H), 3.94-4.02 (m, 3 H), 3.62-3.70 (m, 1 H), 3.30-3.38 (m, 2 H), 2.95 (s, 3 H), 2.42-2.50 (m, 1 H), 1.98-2.08 (m, 2 H), 1.82-1.90 (m, 1 H), 1.20 (t, 3 H). MS (m/z): 536.6
134		MS (m/z): 536.6

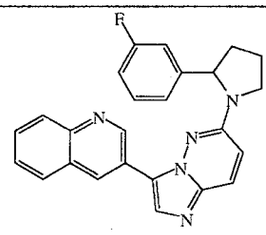
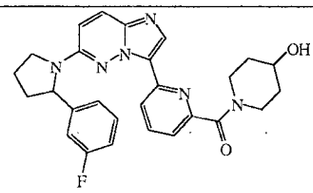
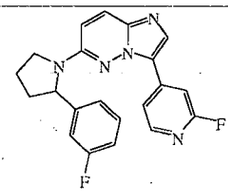
103

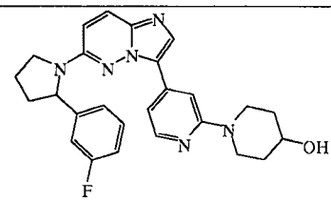
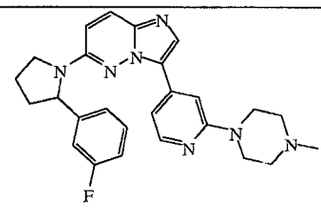
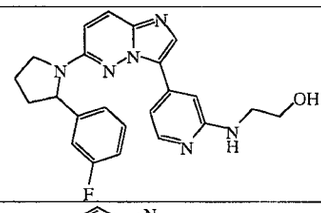
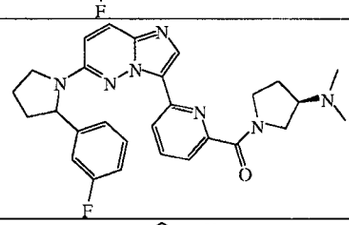
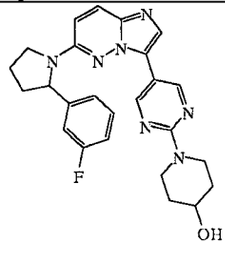
135		1H NMR (DMSO-d6) 8.02 (s, 1 H), 7.88 (d, 1 H, J=10 Hz), 7.48-7.62 (bs, 1 H), 7.40-7.47 (m, 1 H), 7.33-7.40 (m, 1 H), 7.12-7.17 (m, 2 H), 6.99-7.06 (m, 1H), 6.75-6.87 (bs, 1H), 6.29 (d, 1 H, J=8.4 Hz), 5.13-5.18 (q, 1 H), 4.72 (s, 4 H), 4.12 (s, 4 H), 3.94-4.03 (m, 1 H), 3.60-3.70 (m, 1 H), 2.40-2.48 (m, 1 H), 1.98-2.06 (m, 2 H), 1.82-1.90 (m, 1 H). MS (m/z): 457.5
136		1H NMR (DMSO-d6) 8.52 (d, 1 H, J=5.2 Hz), 8.32 (s, 1 H), 8.21 (d, 1 H, J=7.6 Hz), 7.94 (d, 1 H, J=10 Hz), 7.86-7.92 (m, 1 H), 7.74 (d, 1 H, J=4.8 Hz), 7.36-7.44 (m, 1 H), 7.14-7.22 (m, 2 H), 7.00-7.08 (m, 1H), 6.82-6.96 (bs, 1 H), 5.17-5.23 (q, 1 H), 4.76 (s, 4 H), 4.29 (s, 4 H), 3.98-4.06 (m, 1 H), 3.64-3.74 (m, 1 H), 2.43-2.50 (m, 1 H), 2.00-2.10 (m, 2 H), 1.84-1.92 (m, 1 H). MS (m/z): 535.6
137		MS (m/z): 414.4
138		1H NMR methanol-d4, d (ppm) 8.05 (b, 2H), 7.65 (b, 1H), 7.46 (s, 1H), 7.38 (m, 1H), 7.28 (m, 1H), 7.18 (m, 1H), 7.10 (m, 2H), 6.87 (td, 1H), 5.20 (s, 1H), 4.18 (dd, 1H), 4.02 (m, 3H), 3.76 (td, 1H), 3.60 (m, 1H), 3.53 (s, 2H). MS (m/z): 430.4
139		MS (m/z): 460.5

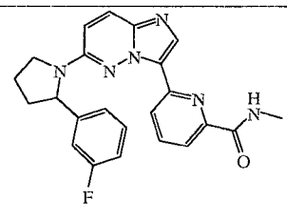
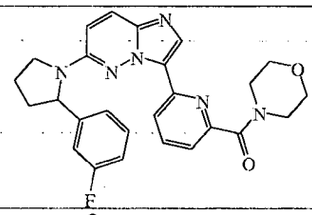
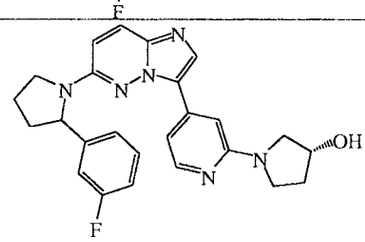
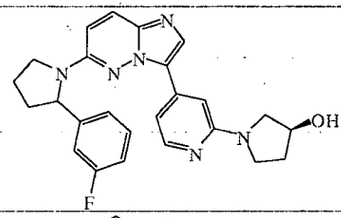
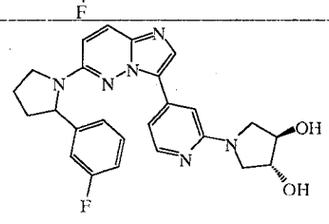
140		MS (m/z): 376.4
141		1H NMR methanol-d4, d (ppm) 7.98 (s, 1H), 7.68 (d, 1H), 7.52 (d, 1H), 7.44 (t, 1H), 7.31 (m, 2H), 7.19 (t, 2H), 7.09 (m, 2H), 6.64 (d, 1H), 5.09 (t, 1H), 4.11 (m, 3H), 4.01 (m, 2H), 3.74 (m, 3H), 3.63 (m, 1H), 3.03 (m, 2H), 1.83 (m, 2H), 1.41 (m, 2H) MS (m/z): 457.5
142		1H NMR methanol-d4, d (ppm) 8.12 (s, 1H), 7.85 (m, 1H), 7.60 (m, 2H), 7.27 (m, 4H), 6.97 (m, 1H), 6.75 (m, 1H), 5.25 (t, 1H), 4.28 (m, 4H), 4.14 (m, 3H), 3.93 (m, 2H), 3.73 (m, 1H), 2.83 (m, 1H), 1.92 (m, 2H), 1.82 (m, 1H), 1.41 (m, 1H). MS (m/z): 487.5
143		1H NMR methanol-d4, d (ppm) 8.45 (s, 1H), 8.17 (d, 1H), 7.79 (d, 1H), 7.67 (m, 2H), 7.36 (m, 1H), 7.26 (m, 2H), 7.13 (d, 1H), 6.98 (m, 2H), 5.40 (m, 1H), 4.63 (m, 2H), 4.34 (m, 1H), 4.15 (m 3H), 3.88 (m, 1H), 3.79 (m, 1H), 3.06 (td, 2H), 2.31 (s, 3H), 2.12 (m, 2H), 1.85 (m, 2H). MS (m/z): 539.6
144		MS (m/z): 419.5
145		MS (m/z): 534.7

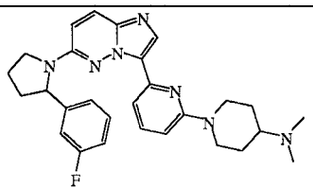
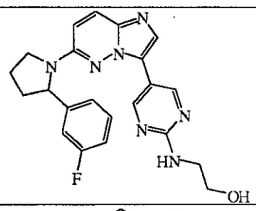
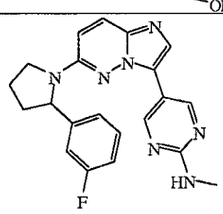
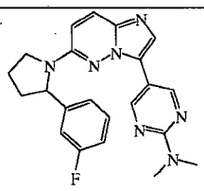
146		1H NMR methanol-d4, d (ppm) 8.52 (s, 1H), 8.15 (d, 1H), 7.81 (m, 3H), 7.36 (m, 1H), 7.25 (m, 2H), 7.00 (m, 2H), 5.40 (m, 1H), 4.34 (dd, 1H), 4.15 (m, 4H), 3.89 (td, 2H), 3.74 (m, 5H), 3.51 (m, 4H), 3.33 (m, 2H), 3.13 (s, 3H). MS (m/z): 566.7
147		1H NMR methanol-d4, d (ppm) 8.33 (s, 1H), 8.27 (s, 1H), 8.03 (d, 1H), 7.65 (d,1H), 7.54 (m, 2H), 7.25 (m, 1H), 7.15 (m, 2H), 6.87 (m, 2H), 5.29 (m, 1H), 4.45 (m, 2H), 4.24 (dd, 1H), 4.04 (m, 3H), 3.77 (td, 1H), 3.66 (m, 1H), 3.20 (m, 1H), 3.00 (m, 2H), 1.99 (m, 2H), 1.75 (m, 2H). MS (m/z): 526.6
148		1H NMR methanol-d4, d (ppm) 8.50 (s, 1H), 8.31 (s, 1H), 8.00 (d, 1H), 7.61 (d,1H), 7.54 (m, 2H), 7.25 (m, 1H), 7.15 (m, 2H), 6.84 (m, 2H), 5.28 (m, 1H), 4.36 (m, 2H), 4.21 (dd, 1H), 4.04 (m, 3H), 3.77 (td, 1H), 3.66 (m, 1H), 3.03 (m, 3H), 2.08 (m, 2H), 1.81 (m, 2H). MS (m/z): 527.6
149		1H NMR (400 MHz, D6 acetone) ppm: 8.40 (br s 1H), 8.35 (d, J=8.1 Hz, 1H), 7.85 (d, J=7.0 Hz, 1H), 7.62(d, J=6.2 Hz, 1H), 7.52-7.40 (m, 1H), 7.38-7.28 (m, 1H), 7.14 (d, J = 6.0 Hz, 1H),7.04 (app d, J = 8.0 Hz, 1H), 6.85 (app dt, J = 8.4, 3.5 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 5.58 (d, J= 6.7 Hz, 1H), 4.31 (app dt, J = 6.8, 2.5 Hz, 2H), 4.22-4.04 (m, 2H), 3.52-3.48 (m, 1H),3.28-3.07 (m, 3H), 2.39-2.31 (m, 1H), 2.22-2.10 (m, 1H), 1.97-1.77 (m, 4H), 1.67-1.42 (m, 4H). MS (m/z): 473.6
150		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.45 (br s 1H), 8.06 (d, J=8.4 Hz, 1H), 7.92 (d, J=7.4 Hz, 1H), 7.81-7.77 (m. 2H), 7.42-7.36(m, 2H), 7.14 (app d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 6.81 (app t, J = 7.2 Hz, 1H), 6.18 (br s, 2H), 5.21 (d, J= 7.7 Hz, 1H), 3.95 (app q, J = 5.5

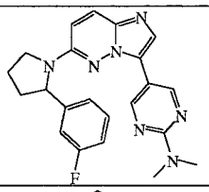
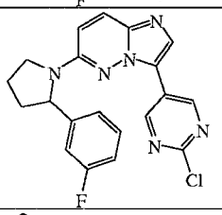
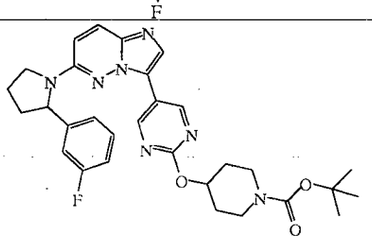
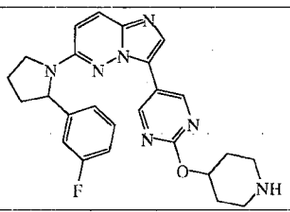
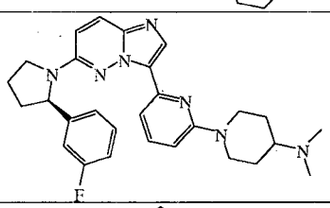
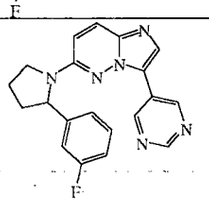
		Hz, 1H), 3.67 (app q, J = 7.5 Hz, 1H), 2.62-2.45 (m, 2H), 2.22-2.02 (m, 1H), 1.95 (app t, J = 2.5 Hz, 1H). MS (m/z): 403.4
151		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.15 (br s 1H), 7.90-7.83 (m, 1H), 7.58-7.52 (m, 1H), 7.34 (app q, J = 8.0 Hz, 1H), 7.10 (d, J = 7.2 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.89 (app t, J = 6.2 Hz, 2H), 6.82 (br s, 1H), 6.52 (app d, J = 4.6 Hz, 1.0 H), 5.19 (d, J= 7.7 Hz, 1H), 4.05 (app q, J = 6.2 Hz, 1H), 3.74 (app q, J = 8.5 Hz, 1H), 2.64-2.40 (m, 2H), 2.20-2.00 (m, 1H), 1.95 (app t, J = 2.5 Hz, 1H). MS (m/z): 376.4
152		MS (m/z): 404.4
153		MS (m/z): 428.4
154		MS (m/z): 426.5
155		MS (m/z): 410.5
156		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.05-7.98 (m, 2H), 7.83 (app d, J = 6.8 Hz, 2H), 7.28(app q, J = 6.2 Hz, 2H), 7.14 (br s, 1H), 6.98 (d, J = 7.0 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H),

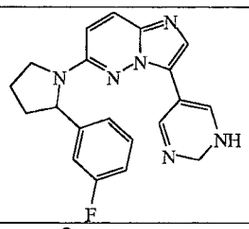
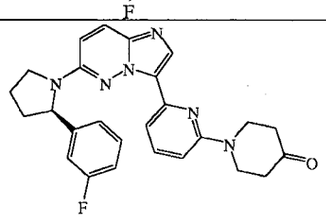
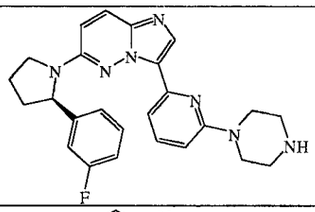
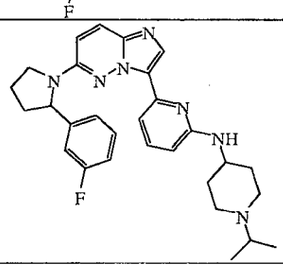
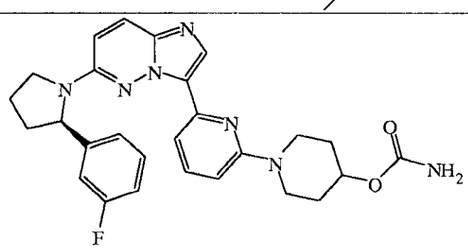
		6.85 (app t, J = 6.2 Hz, 2H), 5.02 (dd, J= 7.4, 2.2 Hz, 1H), 3.87 (app q, J = 5.5 Hz, 1H), 3.61 (app q, J = 8.5 Hz, 1H), 2.99 (s, 3H), 2.44-2.38(m, 2H), 2.06-1.95(m, 2H). MS (m/z): 437.5
157		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.14 (app t, J = 5.6 Hz, 2H), 8.12 (br s, 1H), 8.02 (br s, 1H), 7.98 (app dt, J = 6.8, 1.2 Hz, 2H), 7.78 (app dt, J = 6.8, 1.2 Hz, 2H), 7.30-7.25 (m, 2H), 7.15(app d, J = 6.1 Hz, 1H), 7.04 (dd, J= 8.2, 1.9 Hz, 1H), 6.96 (t, J = 7.0 Hz, 1H), 5.22 (d, J= 7.94 Hz, 1H), 4.05 (m, 1H), 3.78 (app q, J = 7.5 Hz, 1H), 2.57-2.54 (m, 1H), 2.14-1.99(m, 3H). MS (m/z): 410.5
158		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.30 (br s, 1H), 8.14 (app d, J = 2.6 Hz, 2H), 7.89 (br s, 1H), 7.54 (d, J = 6.8 Hz, 1H), 7.35 (q, J = 7.2 Hz, 1H), 7.25 (br s, 1H), 7.16 (d, J = 6.9 Hz, 1H), 7.08 (d, J= 8.2 Hz, 1H), 6.96 (t, J = 7.4 Hz, 1H), 5.23 (dd, J= 7.94, 1.9 Hz, 1H), 4.15 (br d, J =7.8 Hz, 1H), 4.05 (app q, J = 6.8 Hz, 1H), 3.87 (app q, J = 6.7 Hz, 1H), 3.72 (q, J = 7.5 Hz, 1H), 3.67-3.63 (m, 1H), 3.33-3.12 (m, 4H), 2.57-2.54 (m, 1H), 2.14-1.99(m, 2H), 1.65-1.59 (m 2H). MS (m/z): 487.5
159		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.28 (d, J = 6.2 Hz, 1H), 8.20 (br s, 1H), 8.04 (app d, J = 6.6 Hz, 1H), 7.74 (s, 1H), 7.67 (s, 1H), 7.34 (q, J = 6.8 Hz, 1H), 7.22-7.14 (m, 2H), 7.03 (dd, J = 6.9, 1.2 Hz, 1H), 6.97 (dt, J = 6.4, 1.2 Hz, 1H), 5.18 (dd, J= 6.7, 1.9 Hz, 1H), 4.00 (app q, J = 5.8 Hz, 1H), 3.72 (app q, J = 6.4 Hz, 1H), 2.54-2.47 (m, 1H), 2.13-2.03 (m, 2H), 1.97-1.87 (m, 1H). MS (m/z): 378.4

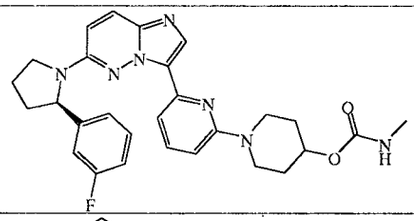
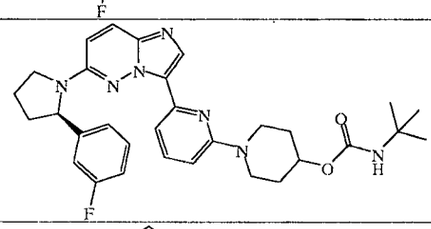
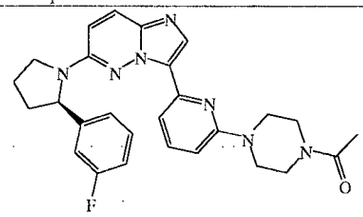
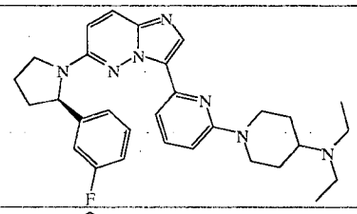
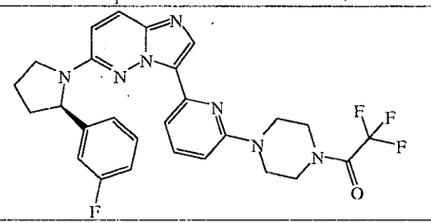
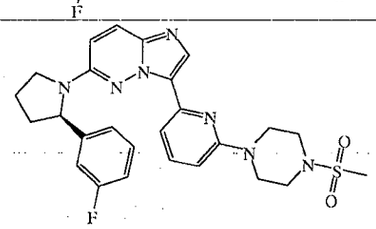
160		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.18 (s, 1H), 8.04 (d, J = 6.9 Hz, 1H), 7.78 (s, 1H), 7.38 (q, J = 7.2 Hz, 1H), 7.28-7.19 (m, 1H), 7.10 (dd, J = 6.2, 1.2 Hz, 1H), 6.94 (app d, J = 6.8 Hz, 2H), 6.82-6.74 (m, 2H), 5.32 (app t, J= 2.9 Hz, 1H), 5.12 (dd, J= 7.4, 1.6 Hz, 1H), 4.01-3.86 (m, 4H), 3.74 (app q, J = 6.8 Hz, 1H), 3.52 (app t, J = 6.0 Hz, 1H), 2.58-2.50 (m, 1H), 2.20-2.18 (m, 1H), 2.15-1.98 (m, 6H), 1.67-1.61 (m, 1H). MS (m/z): 459.5
161		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.08 (d, J= 7.1 Hz, 1H), 7.92 (s, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.62 (s, 1H), 7.41 (q, J = 8.2 Hz, 1H), 7.18 (app t, J = 8.9 Hz, 2H), 7.08 (d, J = 6.8 Hz, 1H), 6.95 (t, J = 5.8 Hz, 1H), 6.68 (dd, J = 7.4, 1.8 Hz, 1H), 5.17 (d, J= 6.9 Hz, 1H), 3.98 (dd, J= 7.6, 2.6 Hz, 1H), 3.72 (app q, J = 7.8 Hz, 1H), 3.58-3.51 (m, 4H), 2.46-2.40 (m, 4H), 2.20 (s, 3H), 2.08-2.03 (m, 1H). MS (m/z): 458.5
162		MS (m/z): 419.5
163		MS (m/z): 500.6
164		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.82 (s, 1H), 7.73 (s, 1H), 7.72-7.70 (m, 2H), 7.35 (q, J = 6.9 Hz, 1H), 7.09 (d, J = 6.9 Hz, 1H), 7.02 (d, J = 5.6 Hz, 1H), 6.89 (t, J = 5.8 Hz, 1H), 6.69 (dd, J = 6.9, 1.3 Hz, 1H), 5.07 (d, J= 7.9 Hz, 1H), 4.48-4.42 (m, 2H), 3.92-3.89 (m, 1H), 3.85-3.80 (m, 1H), 3.66 (q, J= 7.1 Hz, 1H), 3.38-3.32 (m, 2H), 2.48-2.42 (m,

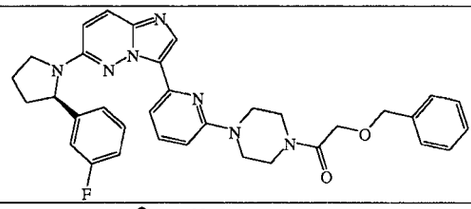
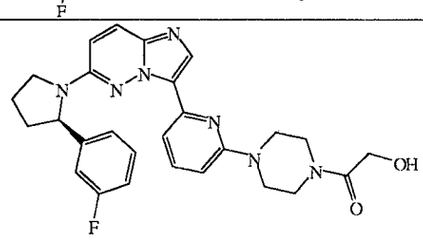
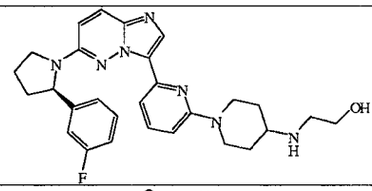
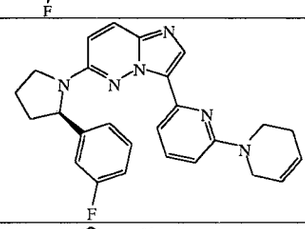
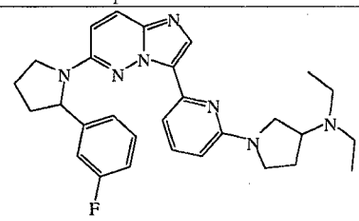
		1H), 2.13-2.03 (m, 4H), 1.50-1.45 (m, 2H). MS (m/z): 460.5
165		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.58 (s, 1H), 8.30-8.16 (m, 2H), 8.08 (app d, J = 6.9 Hz, 1H), 7.91 (br s, 1H), 7.42 (q, J = 5.9 Hz, 1H), 7.22 (br s, 1H), 7.19 (dd, J = 6.9, 1.2 Hz, 1H), 7.02 (d, J = 7.2 Hz, 1H), 6.99(dt, J = 6.8, 1.0 Hz, 1H), 5.24 (dd, J= 6.8, 1.9 Hz, 1H), 4.04 (app q, J = 6.4 Hz, 1H), 3.72 (app q, J = 5.4 Hz, 1H), 2.92 (d, J = 4.2 Hz, 3H), 2.54-2.47 (m, 1H), 2.19-2.10 (m, 2H), 2.03-1.95 (m, 1H). MS (m/z): 417.5
166		MS (m/z): 473.5
167		1H NMR (600 MHz, D3 acetonitrile) ppm: 8.08 (s, 1H), 8.04 (s, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.52-7.45 (m, 2H), 7.41 (app d, J = 3.2 Hz, 1H), 7.18 (br s, 2H), 7.01 (t, J = 6.1 Hz, 1H), 6.72(d, J = 5.8 Hz, 1H), 5.27 (d, J= 6.9 Hz, 1H), 4.58 (br s, 1H), 4.11 (app t, J = 6.8 Hz, 1H), 4.04 (d, J = 4.5 Hz, 1H), 3.82 (q, J = 4.9 Hz, 1H), 3.77-3.54 (m, 3H), 3.52-3:48 (m, 1H), 2.66-2.60 (m, 1H), 2.20-2.01 (m, 4H). MS (m/z): 445.5
168		MS (m/z): 445.5
169		1H NMR (600 MHz, D3 acetonitrile) ppm: 8.06 (br s, 2H), 7.74 (d, J = 7.2 Hz, 1H), 7.48-7.42 (m, 2H), 7.28 (d, J = 7.2 Hz, 1H), 7.18 (br s, 2H), 7.01 (t, J = 6.8 Hz, 1H), 6.72 (d, J = 6.8 Hz, 1H), 5.23 (d, J= 6.4 Hz, 1H), 4.58 (br s, 1H), 4.31 (br s,

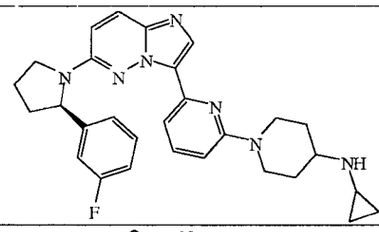
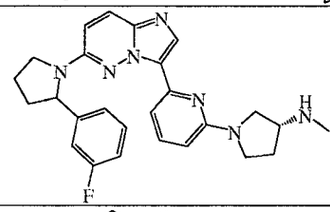
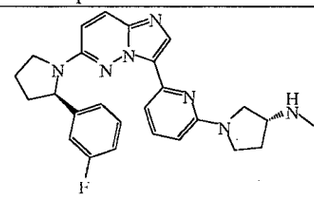
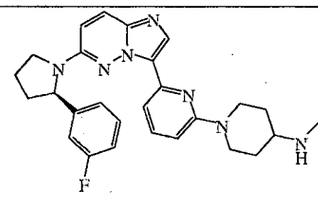
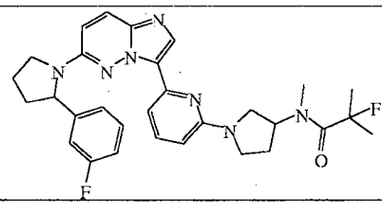
		2H), 4.11 (app t, J = 6.8 Hz, 1H), 3.88 (d, J = 4.5 Hz, 1H), 3.82 (t, J = 5.9 Hz, 1H), 3.61-3.59 (m, 2H), 3.21 (app d,J= 5.5 Hz, 1H), 2.63-2.58 (m, 1H), 2.16-2.00 (m, 4H). MS (m/z): 461.5
170		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.26 (s, 1H), 8.04 (br d, J = 6.2 Hz, 1H), 7.48 (br s, 1H), 7.39 (q, J = 7.5 Hz, 1H), 7.20 (s, 1H), 7.10-7.04 (m, 2H), 7.03 (d, J = 7.0 Hz, 1H), 6.99 (dt, J = 6.9, 1.2 Hz, 1H), 6.82 (d, J = 6.8 Hz, 1H), 5.13 (dd, J= 6.4, 1.2 Hz, 1H), 4.58 (br s, 2H), 4.02-4.00 (m, 1H), 3.62 (app q, J = 6.9 Hz, 1H), 3.22 (app t, 1H), 2.82 (app t, J= 6.5 Hz, 1H), 2.75 (br s, 6H), 2.62-2.52 (m, 2H), 2.48-2.38 (m, 3H), 2.11-2.00 (m, 3H), 1.84-1.80 (m, 1H). MS (m/z): 486.6
171		MS (m/z): 420.5
172		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.82 (s, 2H), 8.33 (d, 7.8 Hz, 1H), 8.18 (br s, 1H), 7.43-7.32 (m, 2H), 7.15 (d, J = 6.9 Hz, 1H), 7.04 (dd, J = 6.9, 1.5 Hz, 1H), 6.92 (t, J = 7.0 Hz, 1H), 5.27 (dd, J= 7.4, 2.2 Hz, 1H), 4.28-4.22 (m, 1H), 3.89 (app q, J = 6.7 Hz, 1H), 3.05(s, 3H), 2.71-2.62 (m, 1H), 2.23-2.03 (m, 2H), 2.01-1.99 (m, 1H). MS (m/z): 390.4
173		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.62 (s, 2H), 8.06 (d, 7.9 Hz, 1H), 7.94 (br s, 1H), 7.23 (q, J = 6.4 Hz, 1H), 7.04 (app t, J = 6.5 Hz, 1H), 6.94 (d, J = 7.2 Hz, 1H), 6.82 (t, J = 6.1 Hz, 1H), 5.21 (dd, J= 7.0, 2.2 Hz, 1H), 3.92(ddd, J = 6.6 Hz, 4.3 Hz, 1.9 Hz, 1H), 3.71-3.65 (m, 1H), 3.10 (s, 6H), 2.51-2.43 (m, 1H), 2.23-2.03 (m, 2H), 2.01-1.99 (m, 1H).

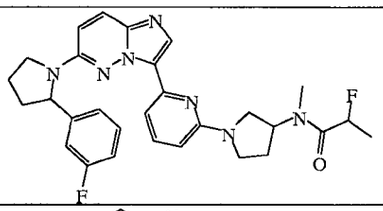
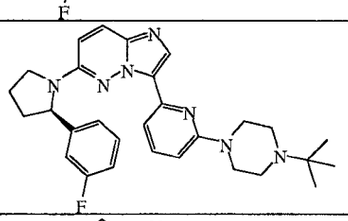
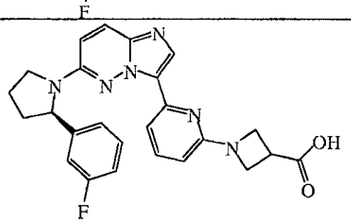
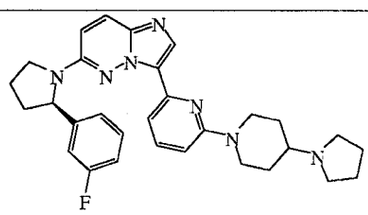
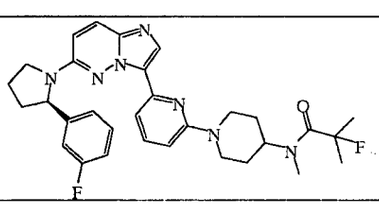
		MS (m/z): 404.5
174		MS (m/z): 486.6
175		MS (m/z): 395.8
176		1H NMR (400 MHz, D6 acetone) ppm: 8.91 (s, 2H), 7.80 (s, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.22 (q, J = 6.8 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 7.4 Hz, 1H), 6.82 (t, J = 7.1 Hz, 1H), 6.67 (d, J = 7.2 Hz, 1H), 5.11 (t, J = 5.4 Hz, 1H), 5.02 (dd, J= 7.0, 2.2 Hz, 1H), 3.96-3.87 (m, 1H), 3.74-3.63 (m, 2H), 3.01 (app q, J = 5.2 hz, 1H), 2.72 (s, 9H), 2.43-2.38 (m, 1H), 2.13-1.99 (m, 4H), 1.67-1.58 (m, 3H), 1.54-1.48 (m, 2H). MS (m/z): 560.6
177		MS (m/z): 460.5
178		MS (m/z): 486.6
179		1H NMR (400 MHz, D6 DMSO) ppm: 9.30 (s, 2H), 9.06 (s, 1H), 8.20 (s, 1H), 7.93 (d, J =7.9 Hz, 1H), 7.35 (q, J = 6.4 Hz, 1H), 7.15-7.05 (m, 2H), 7.03 (app t, J = 6.9 Hz, 1H), 6.88 (d, J = 7.2 Hz, 1H), 5.19 (dd, J= 7.0, 2.2 Hz, 1H), 3.99 (app d, J = 6.9 Hz, 1H), 3.66 (m, 1H), 3.10 (s, 6H), 2.51-2.43 (m, 1H), 2.23-2.03 (m, 2H), 2.01-1.99 (m, 1H). MS (m/z): 361.4

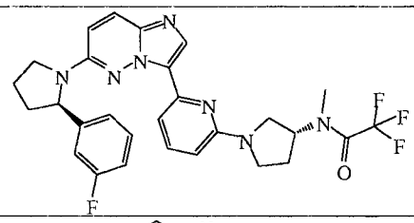
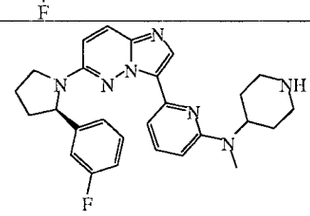
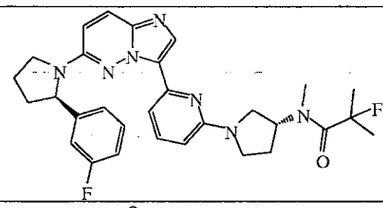
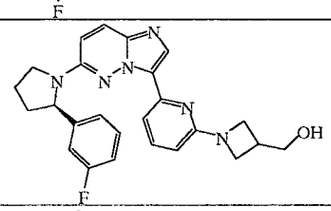
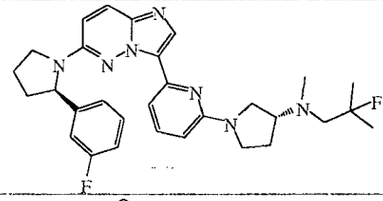
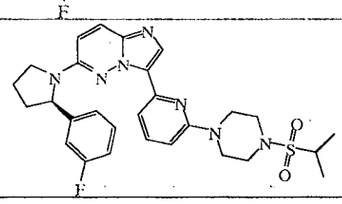
180		MS (m/z): 363.4
181		1H NMR (400 MHz, D6 acetone) ppm: 8.45 (s, 1H), 8.28 (d, J = 6.7 Hz, 1H), 7.64-7.58 (m, 2H), 7.38 (app q, J = 6.9 Hz, 1H), 7.29 (br s, 1H), 7.21 (d, J = 7.3 Hz, 1H), 7.19 (d, J = 6.9 Hz, 1H), 7.02-6.97 (m, 2H), 5.34 (dd, J= 6.8, 2.49 Hz, 1H), 4.22-4.17 (m, 1H), 4.08 (app t, J = 8.4 Hz, 4H), 3.82 (app q, J = 6.4 Hz, 1H), 2.62-2.57 (m, 1H), 2.48 (app t, J = 8.4 Hz, 4H), 2.21-2.10 (m, 2H), 2.03-1.99 (m, 1H). MS (m/z): 457.5
182		MS (m/z): 444.5
183		MS (m/z): 500.6
184		1H NMR (400 MHz, D6 acetone) ppm: 8.51 (s, 1H), 8.38 (d, J = 6.4 Hz, 1H), 7.54 (br s, 1H), 7.42 (app q, J = 6.3 Hz, 1H),7.28 (d, J = 6.9 Hz, 1H), 7.02 (dt, J = 6.7, 1.6 Hz, 1H), 6.92 (d, J = 6.9 Hz, 1H), 5.82 (br s, 2H), 5.37 (dd, J= 6.0, 1.5 Hz, 1H), 4.88-4.77 (m, 1H), 4.32-4.26 (m, 2H), 3.92 (app q, J = 7.4 Hz, 4H), 3.42 (app dt, J = 6.8, 1.9 Hz, 1H), 2.68-2.63 (m, 1H), 2.38-2.22 (m, 2H), 2.06-2.02 (m, 1H), 2.00-1.97 (m, 1H), 1.64-1.55 (m, 2H). MS (m/z): 502.6

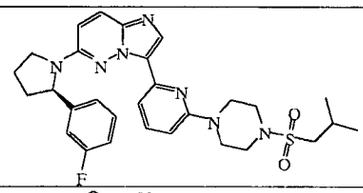
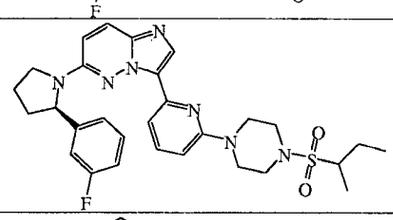
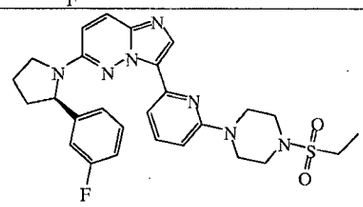
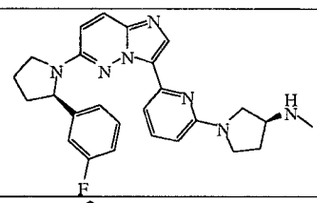
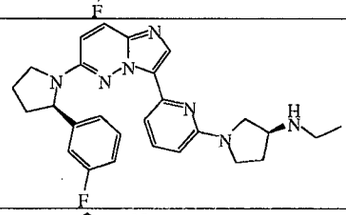
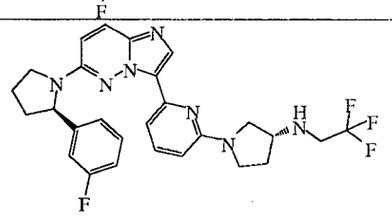
185		MS (m/z): 516.6
186		MS (m/z): 558.7
187		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.28 (s, 1H), 8.08 (s, 1H), 7.54 (br s, 1H), 7.38 (app q, J = 6.8 Hz, 1H), 7.35-7.26 (m, 2H), 7.18 (d, J = 6.9 Hz, 1H), 7.10 (d, J = 6.9 Hz, 1H), 7.00 (dt, J = 7.2, 1.9 Hz, 1H), 6.82 (d, J = 6.9 Hz, 1H), 5.22 (dd, J= 6.4, 1.7 Hz, 1H), 4.08-4.02 (m, 1H), 3.76 (app q, J = 7.0 Hz, 1H), 3.68-3.62 (m, 4H), 3.59-3.54 (m, 4H), 2.60-2.48 (m, 1H), 2.38-2.22 (m, 2H), 2.14-2.02 (m, 1H), 1.97 (s, 3H). MS (m/z): 486.6
188		MS (m/z): 514.7
189		MS (m/z): 540.5
190		1H NMR (400 MHz, D6 DMSO) ppm: 8.38 (s, 1H), 8.04 (d, J = 7.5 Hz, 1H), 7.56 (br s, 1H), 7.39 (app q, J = 7.2 Hz, 1H), 7.23 (d, J = 7.7 Hz, 1H), 7.17-7.11 (m, 2H), 7.05 (t, J = 7.9 Hz, 1H), 6.98 (d, J = 7.9 Hz, 1H), 6.90 (br d, J = 8.2 Hz, 1H), 5.22 (dd, J=7.4, 2.2 Hz, 1H), 4.03-4.01 (m, 1H), 3.71 (br s, 2H), 3.21 (app t, J = 5.6 Hz, 1H), 2.90 (s, 3H), 2.56-2.42 (s,

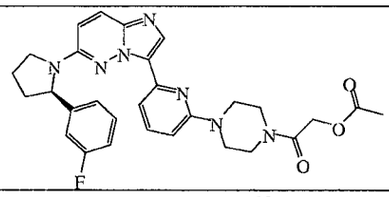
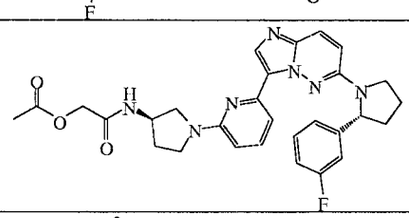
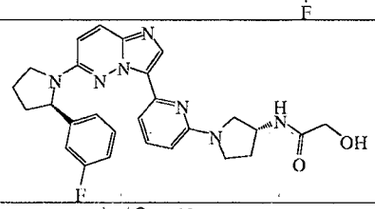
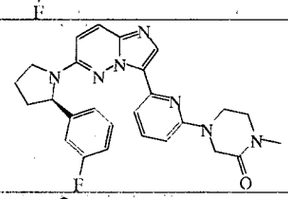
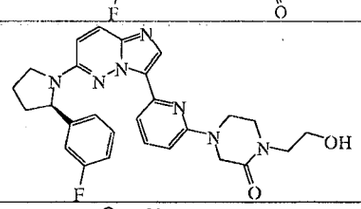
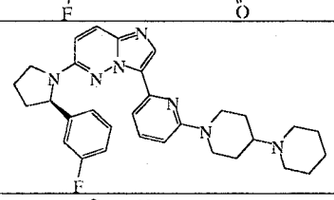
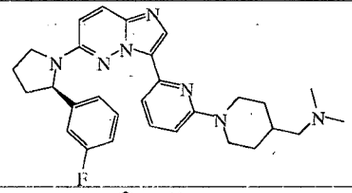
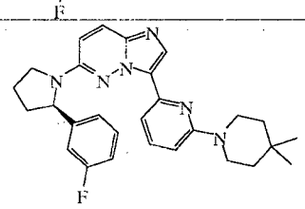
		6H), 2.28-2.12 (m, 2H), 2.04-1.90 (m, 2H). MS (m/z): 522.6
191		MS (m/z): 592.7
192		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.12 (s, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.60 (br s, 1H), 7.49 (t, J = 7.0 hz, 1H), 7.36 (app q, J = 7.4 Hz, 1H), 7.18 (d, J = 7.2 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 6.98 (t, J = 7.7 Hz, 1H), 6.76 (dt, J = 7.2, 1.1 Hz, 1H), 6.67 (d, J = 6.9 Hz, 1H), 5.16 (dd, J=7.8, 2.2 Hz, 1H), 4.18 (br s, 2H), 3.93 (p, J = 3.8 Hz, 1H), 3.67-3.57 (m, 8H), 3.42-3.38 (m, 1H), 2.52-2.45 (m, 1H), 2.18-2.06 (m, 2H), 1.92-1.88 (m, 1H). MS (m/z): 502.6
193		MS (m/z): 502.6
194		MS (m/z): 441.5
195		1H NMR (400 MHz, D6 acetone) ppm: 8.32 (s, 1H), 8.14 (d, J = 7.6 Hz, 1H), 7.55-7.46 (m, 1H), 7.41 (app q, J = 7.4 Hz, 1H), 7.41 (app q, J = 5.4 Hz, 1H), 7.21-7.11 (m, 2H), 7.03 (d, J = 7.6 Hz, 1H), 6.88 (t, J = 7.7 Hz, 1H), 6.42 (d, J = 7.2 Hz, 1H), 5.18 (d, J =5.6 Hz, 1H), 4.10-4.00 (m, 2H), 3.70-3.59 (m, 3H), 3.38-3.04 (m, 8H), 2.50-2.40 (m, 2H), 2.06-1.99 (m, 2H), 2.18-2.06 (m, 2H), 1.42 (t, J = 6.0 Hz, 4H). MS (m/z): 500.6

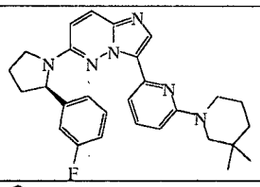
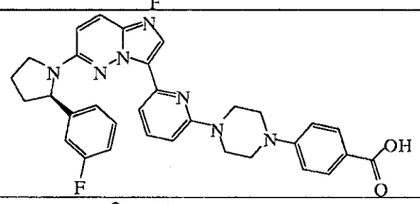
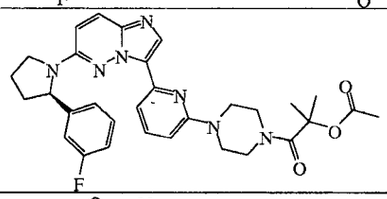
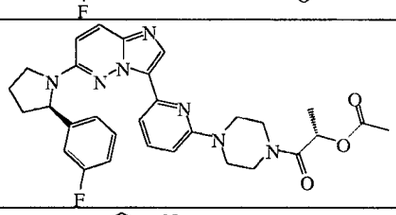
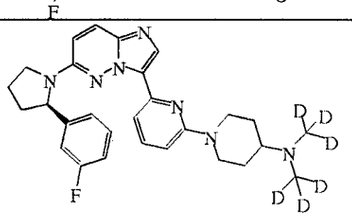
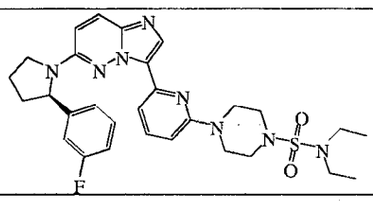
196		MS (m/z): 498.6
197		MS (m/z): 458.5
198		1H NMR (400 MHz, D6 acetone) ppm: 8.28 (d, J = 7.1 Hz, 1H), 8.04 (s, 1H), 7.42 (app q, J = 7.8 Hz, 1H), 7.38 (br s, 1H), 7.28 (d, J = 7.4 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.94 (t, J = 7.7 Hz, 1H), 6.42 (d, J = 6.4 Hz, 1H), 5.28 (d, J =6.6 Hz, 1H), 4.18-4.04 (m, 2H), 3.98 (app d, J = 6.8 Hz, 1H), 3.88-3.62 (m, 4H), 3.48-3.42 (m, 1H), 2.92 (s, 3H), 2.77-2.70 (m, 1H), 2.67-2.56 (m, 1H), 2.32-2.26 (m, 2H), 2.18-2.09 (m, 1H). MS (m/z): 458.5
199		1H NMR (400 MHz, D6 acetone) ppm: 9.43-9.02 (br s, 2H), 8.48 (br s, 1H), 8.35 (s, 1H), 8.56(s, 1H), 7.42 (app q, J = 7.8 Hz, 1H), 7.31 (d, J = 5.6 Hz, 1H), 7.20 (d, J = 7.4 Hz, 1H), 7.02 (dt, J = 8.4, 1.9 Hz, 1H), 6.92 (br d, J = 4.5 Hz, 1H), 5.35 (d, J = 4.6 Hz, 1H), 4.20 (app d, J = 4.9 Hz, 1H), 3.98 (app t, J = 6.8 Hz, 1H), 3.58-3.52 (m, 1H), 3.08-2.98 (m, 3H), 2.82 (s, 3H), 2.71-2.60 (m, 1H), 2.38 (app d, J = 6.8 Hz, 2H), 2.27-2.18 (m, 2H), 2.32-2.26 (m, 2H), 1.88-1.69 (m, 2H). MS (m/z): 472.6
200		MS (m/z): 546.6

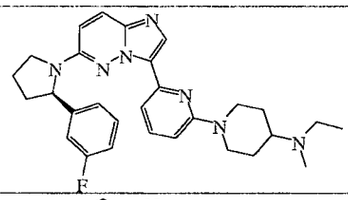
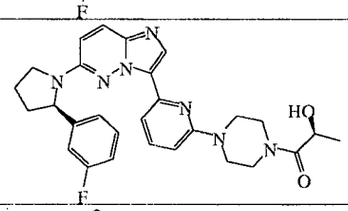
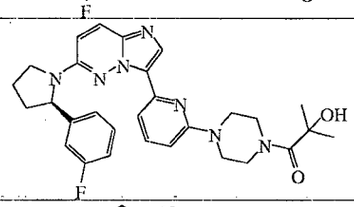
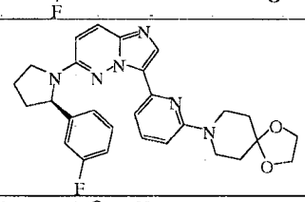
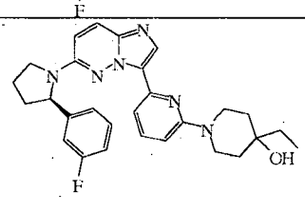
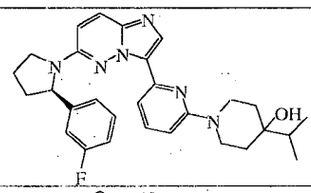
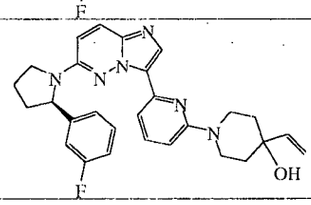
201		MS (m/z): 532.6
202		MS (m/z): 500.6
203		1H NMR (400 MHz, D6 acetone) ppm: 8.28 (br s, 1H), 8.15 (d, J = 7.8 Hz, 1H), 7.56 (br s, 2H), 7.46 (app q, J = 7.8 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.30 (br s, 1H),7.18 (d, J = 7.6 Hz, 1H), 7.04 (dt, J = 7.4, 1.9 Hz, 1H), 6.42 (br d, J = 6.5 Hz, 1H), 5.25 (d, J = 6.6 Hz, 1H), 4.20 (app d, J = 5.9 Hz, 2H), 4.12-4.06 (m, 2H), 3.98 (p, J = 6.8 Hz, 1H), 3.78 (app q, J = 8.2 Hz, 1H), 3.52-3.48 (m, 1H), 2.77-2.68 (m, 1H), 2.28-2.18 (m, 2H), 2.02-1.97(m, 1H). MS (m/z): 459.5
204		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.29 (br s, 1H), 8.19 (d, J = 6.7 Hz, 1H), 7.52 (br s, 2H), 7.38 (app q, J = 7.3 Hz, 1H), 7.24 (br s, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.08 (d, J = 7.9 Hz, 1H), 6.94 (dt, J = 7.6, 1.9 Hz, 1H), 6.82 (d, J = 5.5 Hz, 1H), 5.23 (d, J = 6.9 Hz, 1H), 4.52 (app br d, J = 7.9 Hz, 2H), 4.04-3.99 (m, 1H), 3.78 (q, J = 6.9 Hz, 1H), 3.69-3.62 (m, 1H), 3.33-3.21 (m, 2H), 3.09-3.02 (m, 2H), 2.83 (app t, J = 8.0 Hz, 2H), 2.77-2.50 (m, 6H), 2.28-2.08 (m, 4H), 1.84-1.74 (m, 2H). MS (m/z): 512.6
205		MS (m/z): 560.7

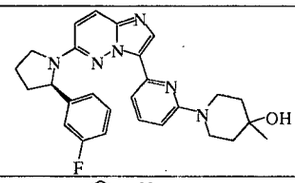
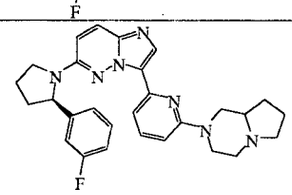
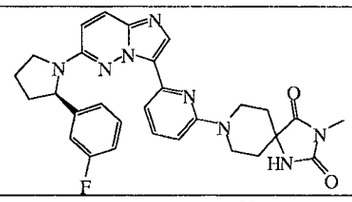
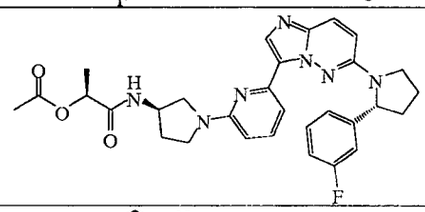
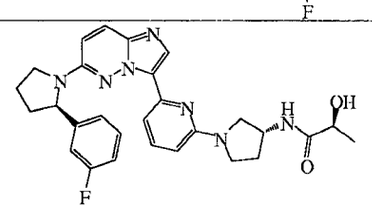
206		MS (m/z): 554.6
207		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.32 (br s, 1H), 8.21 (s, 1H), 8.02 (d, J = 7.4 Hz, 1H), 7.76 (br s, 1H), 7.38 (app t, J = 2.3 Hz, 1H), 7.26 (app q, J = 7.2 Hz, 1H), 7.04-6.97 (m, 2H), 6.92 (d, J = 7.6 Hz, 1H), 6.52 (d, J = 6.5 Hz, 1H), 5.15 (d, J = 6.6 Hz, 1H), 4.78 (dt, J = 6.9, 1.9 Hz, 1H), 3.91-3.79 (m, 1H), 3.58 (q, J = 6.8 Hz, 1H), 3.34 (app d, J = 8.2 Hz, 1H), 3.03 (br q, J = 4.5 Hz, 1H), 2.78 (s, 3H), 2.67-2.48 (m, 4H), 2.28-2.08 (m, 4H), 1.82-1.73 (m, 2H). MS (m/z): 472.6
208		MS (m/z): 546.6
209		MS (m/z): 445.5
210		MS (m/z): 532.6
211		MS (m/z): 550.7

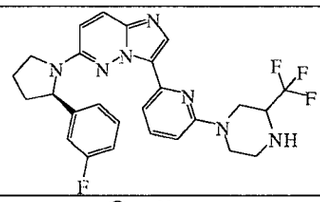
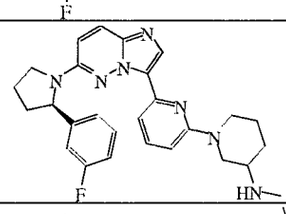
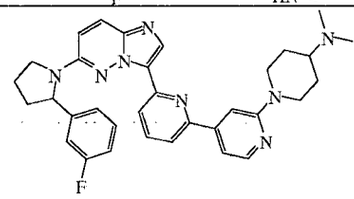
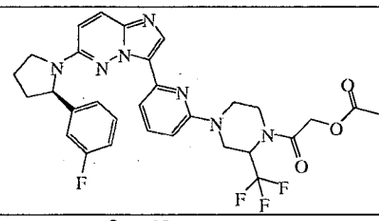
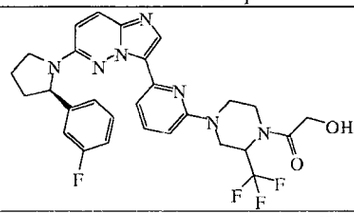
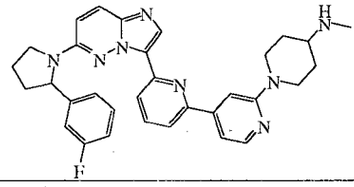
212		MS (m/z): 564.7
213		MS (m/z): 564.7
214		1H NMR (400 MHz, D6 DMSO) ppm: 8.35 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.54 (br s, 2H), 7.39 (q, J = 7.0 hz, 1H), 7.21-7.14 (m, 2H), 7.06 (d, J = 7.0 Hz, 1H), 7.00 (br s, 1H), 6.87 (d, J = 7.8 Hz, 1H), 5.20 (d, J = 6.8 Hz, 1H), 4.08-4.00 (m, 1H), 3.78-3.67 (m, 2H), 3.30-3.26 (m, 1H), 2.67 (q, J = 7.0 Hz, 2H), 2.62-2.54 (m, 6H), 2.42-2.35 (m, 1H), 2.08-2.00 (m, 2H), 1.92-1.88 (m, 1H), 1.25 (t, J = 7.4 Hz, 3H). MS (m/z): 536.6
215		MS (m/z): 458.5
216		MS (m/z): 472.6
217		1H NMR (400 MHz, D6 DMSO) ppm: 8.20 (br s, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.48 (br s, 1H), 7.38 (app q, J = 6.3 Hz, 1H), 7.22 (d, J = 7.2 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 7.04 (d, J = 6.7 Hz, 1H), 6.92 (dt, J = 7.6, 1.9 Hz, 1H), 6.42 (d, J = 7.5 Hz, 1H), 5.25 (d, J = 6.1 Hz, 1H), 4.18-4.04 (m, 3H), 3.92 (dd, 10.1, 6.7 Hz, 1H), 3.78 (q, J = 6.8 Hz, 1H), 3.72 (q, J = 5.8 Hz, 1H), 3.48 (app d, J = 7.2 Hz, 1H), 2.92 (s, 2H), 2.72-2.64 (m, 1H), 2.58-2.53 (m, 2H), 2.21-

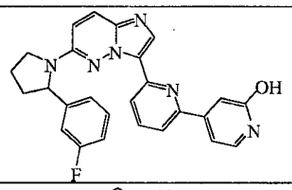
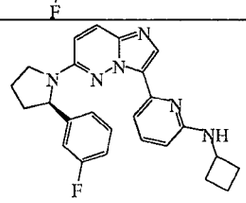
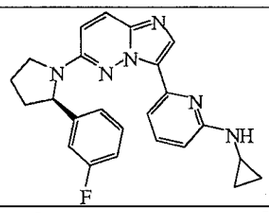
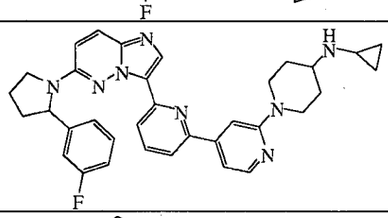
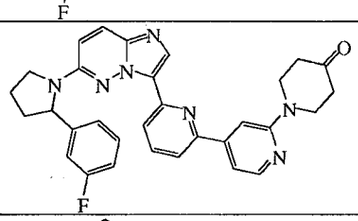
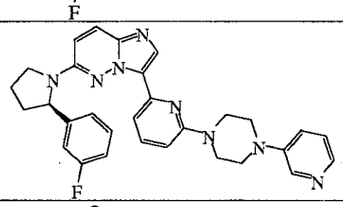
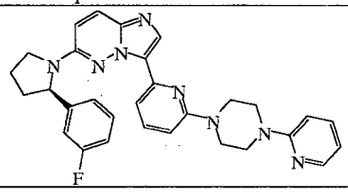
		2.17 (m, 2H), 2.05-1.98 (m, 1H). MS (m/z): 526.5
218		MS (m/z): 544.6
219		MS (m/z): 544.6
220		MS (m/z): 502.6
221		MS (m/z): 472.5
222		MS (m/z): 502.6
223		MS (m/z): 526.7
224		MS (m/z): 500.6
225		1H NMR (400 MHz, D6 DMSO) ppm: 8.34 (s, 1H), 8.04 (br d, J = 6.4 Hz, 1H), 7.46 (br s, 2H), 7.38 (q, J = 7.6 Hz, 1H), 7.24 (s, 1H), 7.18-7.10 (m, 2H), 7.05 (t, J = 6.7 Hz, 1H), 6.82 (d, J = 6.8 Hz, 1H), 5.21 (d, J= 6.5 Hz, 1H), 4.05-4.02 (m, 2H), 3.70 (q, J = 5.6 Hz, 1H), 3.56 (app q, J = 6.2 Hz, 1H),

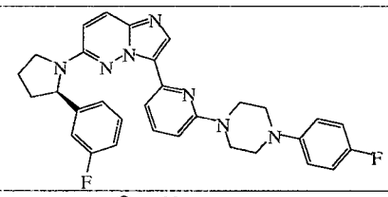
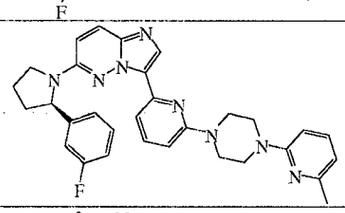
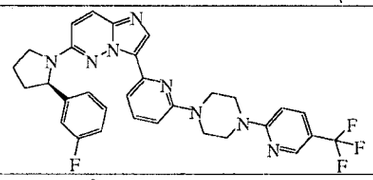
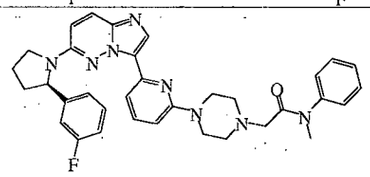
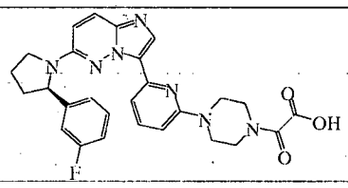
		2.82-2.72 (m, 2H), 2.54-2.44 (m, 1H), 2.08-2.04 (m, 2H), 1.90-1.82 (m, 1H), 1.38-1.35 (m, 4H), 0.95 (s, 6H). MS (m/z): 471.6
226		MS (m/z): 471.6
227		MS (m/z): 564.6
228		MS (m/z): 572.6
229		MS (m/z): 558.6
230		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.20 (s, 1H), 8.00 (br d, J = 6.4 Hz, 1H), 7.40 (br s, 2H), 7.30 (q, J = 7.6 Hz, 1H), 7.04 (d, J= 6.9 Hz, 1H), 6.95 (app d, J = 7.7 Hz, 2H), 6.92 (dt, J = 6.9, 1.2 Hz, 1H), 6.62 (d, J = 6.2 Hz, 1H), 5.03 (dd, J= 6.5, 1.2 Hz, 1H), 4.45-4.40 (m, 2H), 3.98-3.90 (m, 1H), 3.62 (app q, J = 6.9 Hz, 1H), 3.22 (app t, 1H), 2.80 (app t, J= 6.0 Hz, 1H), 2.62-2.52 (m, 2H), 2.48-2.38 (m, 3H), 2.05-1.99 (m, 3H), 1.69-1.67 (m, 1H). MS (m/z): 492.6
231		MS (m/z): 579.7

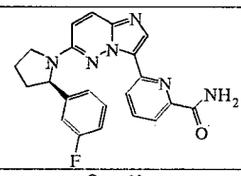
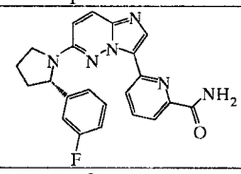
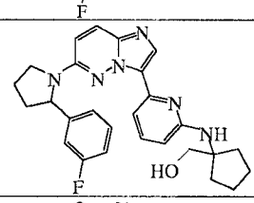
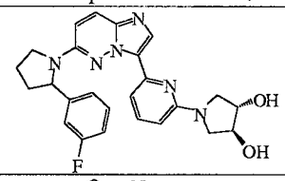
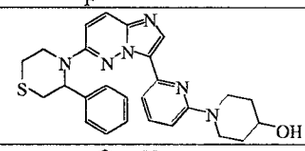
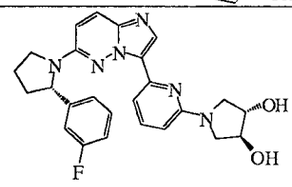
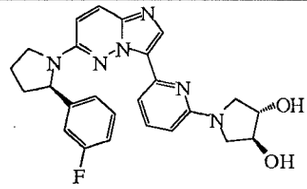
232		MS (m/z): 500.6
233		MS (m/z): 516.6
234		MS (m/z): 530.6
235		MS (m/z): 501.6
236		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.18 (s, 1H), 7.92 (br s, 2H), 7.38 (br s, 2H), 7.28 (app q, J = 7.0 Hz, 1H), 7.08 (s, 1H), 7.02 (d, J = 7.3 Hz, 1H), 6.83 (app t, J = 7.2 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 5.08 (d, J = 6.9 Hz, 1H), 3.95-3.81 (m, 3H), 3.62 (app q, J = 6.2 Hz, 1H), 3.52 (t, J = 4.8 Hz, 1H), 3.22 (app t, J = 5.0 Hz, 2H), 2.55-2.43 (m, 1H), 2.09-1.99(m, 2H), 1.88-1.80 (m, 1H), 1.67 (br s, 1H), 1.50-1.45 (m, 2H), 1.38 (q, J = 5.9 Hz, 2H), 0.80 (t, J= 5.0 Hz, 3H). MS (m/z): 487.6
237		MS (m/z): 501.6
238		MS (m/z): 485.6

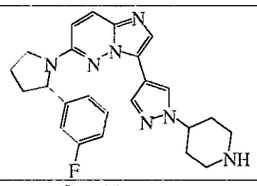
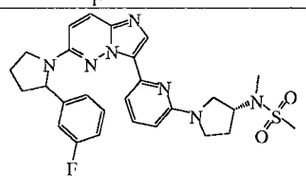
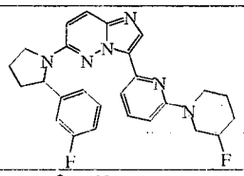
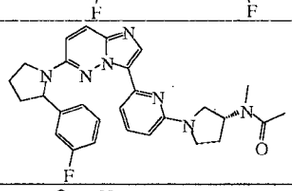
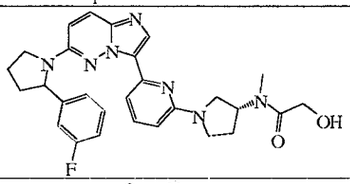
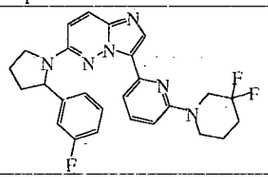
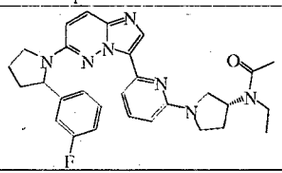
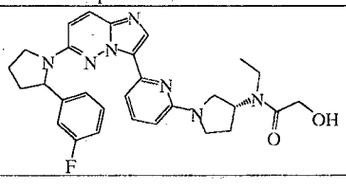
239		MS (m/z): 473.6
240		1H NMR (400 MHz, D6 acetone) ppm: 8.51 (br s, 1H), 8.41 (d, J = 8.8 Hz, 1H), 7.68-7.52 (m, 2H), 7.48 (br s, 1H), 7.38 (app q, J = 7.5 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 6.94 (app dt, J = 7.8, 1.9 Hz, 1H), 6.90 (d, J = 5.6 Hz, 1H), 5.38 (d, J = 6.4 Hz, 1H), 5.05 (dd, J = 5.4 Hz, 1.7 Hz, 1H), 4.72 (app t, J = 7.2 Hz, 1H), 4.22 (d, J = 4.2 Hz, 2H), 4.18 (app q, J = 6.0 Hz, 1H), 4.05 (br s, 1H), 3.98-3.62 (m, 3H), 3.48-3.40 (m, 2H), 3.28-3.22 (m, 1H), 3.18-3.00 (m, 1H), 2.65-2.59 (m, 1H), 2.39-1.99(m, 5H). MS (m/z): 484.6
241		MS (m/z): 541.6
242		MS (m/z): 558.6
243		1H NMR (400 MHz, D6 acetone) ppm: 8.21 (br s, 1H), 7.98-7.82 (m, 2H), 7.45 (app q, J = 6.5 Hz, 2H), 7.40 (app q, J = 6.2 Hz, 1H), 7.22 (d, J = 6.8 Hz, 1H), 7.15 (app d, J = 7.8 Hz, 1H), 6.94 (dt, J = 8.6, 1.9 Hz, 1H), 6.90 (br s, 1H), 6.42 (d, J = 6.2 Hz, 1H), 5.22 (d, J = 6.4 Hz, 1H), 4.54 (app p, J = 6.2 Hz, 1H), 4.22 (app q, J = 5.6 Hz, 2H), 3.78 (q, J = 6.8 Hz, 1H), 3.68-3.62 (m, 1H), 3.58-3.53 (m, 1H), 3.42 (dd, J = 4.8, 1.6 Hz, 1H), 3.21 (app t, J = 7.2 Hz, 2H), 2.62-2.56 (m, 1H), 2.31-2.25 (m, 1H), 2.18-1.99

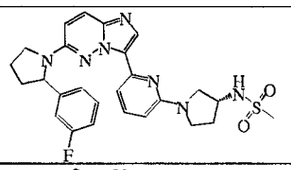
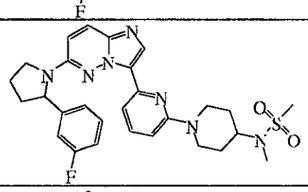
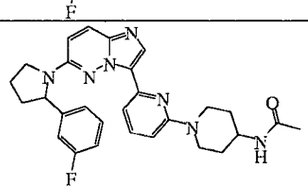
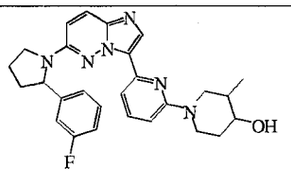
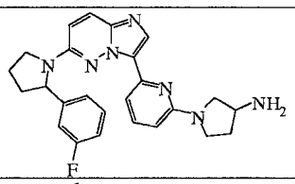
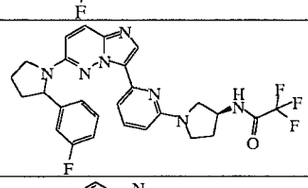
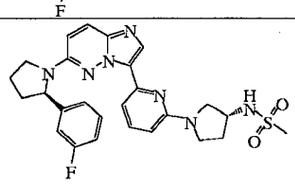
		(m, 3H), 1.42 (d, J = 5.4 Hz, 3H). MS (m/z): 516.6
244		MS (m/z): 512.5
245		MS (m/z): 472.6
246		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.56 (br s, 1H), 8.24 (d, J = 7.2 Hz, 1H), 8.18 (app d, J = 6.5 Hz, 2H), 7.95 (d, J = 6.2 Hz, 1H), 7.88 (br s, 1H), 7.78 (s, 1H), 7.52 (d, J = 6.4 Hz, 1H), 7.38 (app q, J = 6.8 Hz, 1H), 7.28 (br s, 1H), 7.22 (d, J = 7.2 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 6.92 (dt, J = 8.6, 1.9 Hz, 1H), 5.22 (dd, J = 6.9, 1.9 Hz, 1H), 4.51 (app d, J = 10 Hz, 2H), 4.02 (app q, J = 3.6 Hz, 1H), 3.78 (q, J = 6.8 Hz, 1H), 3.48 (t, J = 5.8 Hz, 1H), 3.21 (app t, J = 7.2 Hz, 2H), 2.82 (s, 6H), 2.37-2.25 (m, 2H), 2.18-2.03 (m, 2H), 1.97-1.86 (m, 4H) MS (m/z): 563.7
247		MS (m/z): 612.6
248		MS (m/z): 570.6
249		MS (m/z): 549.7

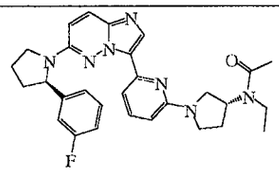
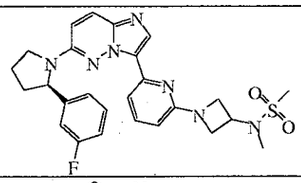
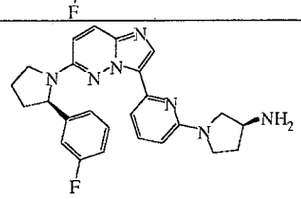
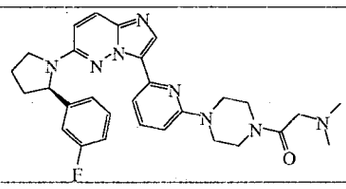
250		MS (m/z): 453.5
251		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.61 (br s, 1H), 8.14 (d, J = 7.7 Hz, 1H), 7.62 (br s, 1H), 7.58 (s, 1H), 7.42 (app q, J = 7.8 Hz, 1H), 7.34-7.29 (m, 1H), 7.26 (d, J = 7.4 Hz, 1H), 7.17 (d, J = 7.2 Hz, 1H), 7.02 (t, J = 8.2 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 5.27 (dd, J = 7.9, 1.9 Hz, 1H), 4.54(p, J = 7.6 Hz, 1H), 4.17 (app q, J = 6.6 Hz, 1H), 3.82 (q, J = 6.8 Hz, 1H), 2.77-2.67 (m, 1H), 2.48-2.35 (m, 2H), 2.38-2.06 (m, 5H), 1.97-1.82 (m, 2H) MS (m/z): 429.5
252		MS (m/z): 415.5
253		MS (m/z): 575.7
254		MS (m/z): 534.6
255		MS (m/z): 521.6
256		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.38 (br s, 2H), 7.58 (s, 1H), 7.42 (q, J = 7.7 Hz, 1H), 7.39 (d, J = 6.7 Hz, 1H), 7.39-7.31 (m, 4H), 7.28 (br s, 1H), 7.22 (d, J = 6.2 Hz, 1H),

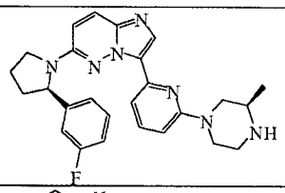
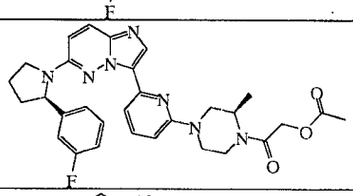
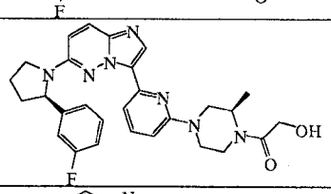
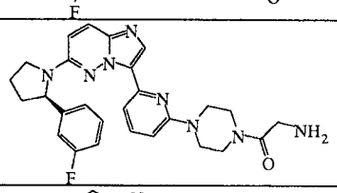
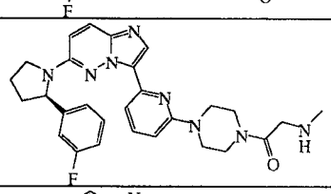
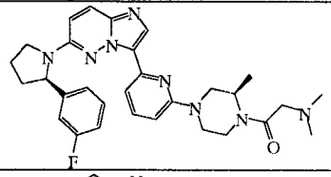
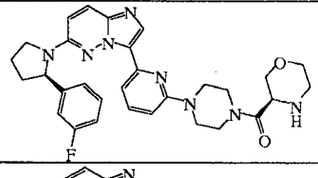
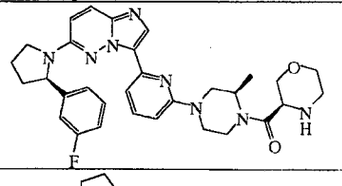
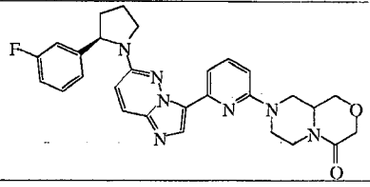
		7.12 (d, J = 7.6 Hz, 1H), 6.98 (t, J = 7.2 Hz, 1H), 6.88 (d, J = 7.2 Hz, 1H), 5.27 (d, J = 7.2 Hz, 1H), 4.22-4.15 (m, 1H), 4.12-4.00 (m, 4H),3.82 (app q, J = 6.7 Hz, 1H), 3.71-3.59 (m, 4H), 2.67-2.59 (m, 1H), 2.28-2.19 (m, 2H), 2.08-2.00 (m, 1H). MS (m/z): 521.6
257		MS (m/z): 538.6
258		MS (m/z): 535.6
259		MS (m/z): 589.6
260		1H NMR (400 MHz, D3 acetonitrile) ppm: 8.35 (br s, 1H), 8.18 (app t, J = 4.5 Hz, 1H), 7.80-7.67 (m, 1H), 7.62 (app t, J = 6.7 Hz, 2H), 7.55 (q, J = 6.2 Hz, 1H), 7.35 (br s, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.15 (app t, J = 8.2 Hz, 2H), 7.08 (dt, J = 7.2, 1.9 Hz, 1H), 6.95 (d, J = 6.9 Hz, 1H), 6.85-6.78 (m, 1H), 5.37 (d, J = 6.2 Hz, 1H), 4.32 (br s, 2H), 4.25-4.11 (m, 4H), 3.82 (s, 3H), 3.62-3.43 (m, 4H), 2.62-2.54 (m, 1H), 2.25-2.14 (m, 2H), 2.08-2.00 (m, 1H). MS (m/z): 591.7
261		MS (m/z): 516.5

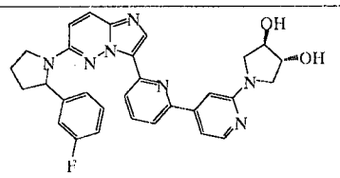
262		MS (m/z): 403.4
263		MS (m/z): 403.4
264		MS (m/z): 473.6
265		MS (m/z): 461.5
266		MS (m/z): 473.6
267		1H NMR 400 MHz (DMSO-d6) 7.983 (s, 1H) 7.822 (d, J = 0.024, 1H) 7.459-7.281 (m, 3H) 7.101-7.081 (m, 2H), 6.966 (dt, J = 0.021, 0.005, 1H), 6.726 (brs, 1H) 6.272 (d, J = 0.021, 1H)5.118-5.098 (m, 2H), 3.976-3.901 (m, 2H) 3.591 (q, J = 0.021, 1H), 3.522 (dd, J = 0.027, 0.009, 2H), 2.380 (m, 1H) 1.969-1.921 (m, 3H), 1.818-1.787 (m, 2H), 1.166 (m, 2H) MS (m/z): 461.5
268		1H NMR 400 MHz (DMSO-d6) 7.981 (s, 1H), 7.823 (d, J = 0.025, 1H), 7.461-7.282 (m, 3H) 7.101 (m, 2H), 6.991 (dt, J = 0.022, 0.005, 1H), 6.725 (brs, 1H) 6.272 (d, J = 0.021, 1H), 5.119 (m, 2H), 3.977-3.901(m, 2H), 3.614 (q, J = 0.021, 1H), 3.516 (dd, J = 0.028, 0.009, 2H), 2.380 (m, 1H), 2.001-1.921 (m, 3H), 1.831-1.792 (m, 2H), 1.167 (m, 2H) MS (m/z): 461.5

269		MS (m/z): 432.5
270		1H NMR 400 MHz (DMSO-d6) 8.019 (s, 1H), 7.828 (d, J = 0.025, 1H), 7.507-7.282 (m, 3H), 7.105 - 7.081 (m,2H), 6.988-6.943 (m, 1H) 6.725 (brs, 1H) 6.356 (d, J = 0.021, 1H), 5.111-5.091 (m, 1H), 4.483 (p, J = 0.019, 1H), 3.952-3.900 (m, 1H), 3.649-3.572(m,1H), 3.441-3.400 (m, 1H), 3.359-3.305 (m, 2H), 2.921 (s, 3H), 2.714 (s, 3H), 2.170-2.041 (m, 2H) 2.002, 1.929(m, 2H), 1.832 - 1.771 (m, 1H) MS (m/z): 536.6
271		MS (m/z): 461.5
272		MS (m/z): 500.6
273		MS (m/z): 516.6
274		MS (m/z): 479.5
275		MS (m/z): 514.6
276		MS (m/z): 530.6

277		MS (m/z): 522.6
278		MS (m/z): 550.7
279		1H NMR 400 MHz (DMSO-d6) 7.981 (s, 1H), 7.829 (d, J = 0.024, 1H), 7.741 (d, J = 0.02, 1H), 7.475-7.217 (m, 3H), 7.098-7.078 (m, 2H), 6.990 (dt, J = 0.022, 0.005, 1H), MS (m/z): 500.6
280		1H NMR 400 MHz (DMSO-d6) 8.041 (s, 1H), 7.902 (d, J = 0.025, 1H), 7.476-7.265 (m, 3H), 7.169 (d, J = 0.02, 2H), 7.055, (t, J = 0.02, 1H), 6.824 (brs, 1H), 6.763 (d, J = 0.022, 1H), 5.177 (d, J = 0.20, 1H), 4.341 (d, J = 0.033, 1H), 4.248 (d, J = 0.031, 1H), 4.018-3.967 (m, 1H), 3.701 (q, J = 0.021, 1H), 3.207-3.133 (m, 1H), 2.878 (t, J = 0.021, 1H), 2.070-1.998 (m, 3H), 1.888-1.830(m, 2H), 1.477-1.292 (m, 3H), 0.988 (d, J = 0.016, 3H) MS (m/z): 473.6
281		MS (m/z): 444.5
282		MS (m/z): 540.5
283		1H NMR 400 MHz (DMSO-d6) 8.061 (s, 1H), 7.871 d, J = 0.019, 1H), 7.386-7.287 (m, 3H), 7.102-7.081 (m, 2H), 6.992 (dt, J = 0.019, 0.004, 1H), 6.831 (brs, 1H), 6.343 (d, J = 0.023, 1H), 5.122 (dd, J = 0.02, 0.006, 1H), 4.108-3.908 (m, 2H), 3.713 (dd, J = 0.026, 0.010, 1H), 3.638 (q, J =

		0.020, 1H), 3.536-3.478 (m, 1H), 3.375 (q, J = 0.018, 1H), 3.313 (dd, J = 0.027, 0.014, 1H), 2.409-2.359 (m, 1H), 2.223 (sextet, J = 0.015, 1H), 2.009-1.776 (m, 4H) MS (m/z): 522.6
284		1H NMR 400 MHz (DMSO-d6) 8.047 (d, J = 0.038, 1H), 7.893 (d, J = 0.025, 1H), 7.571-7.355 (m, 3H), 7.170-7.149 (m, 2H), 7.059 (dt, J = 0.019, 0.004, 1H), 6.802 (brs, 1H), 6.413 (t, J = 0.022, 1H), 5.182 (dd, J = 0.02, 0.006, 1H), 4.879 (p, J = 0.020, 1H), 4.622 (p, J = 0.020, 1H), 4.059-3.967 (m, 1H), 3.699-3.636 (m, 3H), 3.392-3.23 (m, 2H), 2.209-1.994 (m, 7H), 1.90-1.818 (m, 1H), 1.196-1.135(m, 2H), 1.079 (t, J = 0.017, 2H) MS (m/z): 514.6
285		MS (m/z): 522.6
286		1H NMR 400 MHz (DMSO-d6) 7.969 (s, 1H), 7.815 (d, J = 0.024, 1H), 7.397-7.279(m, 3H), 7.096-7.069 (m, 2H), 6.984 (dt, J = 0.022, 0.006, 1H), 6.738 (brs, 1H), 6.256 (d, J = 0.022, 1H), 5.111 (dd, J = 0.020, 0.006, 1H), 3.946-3.895 (m, 1H), 3.628 (q, J = 0.021, 1H), 3.515-3.439 (m, 3H), 3.374-3.314(m, 1H), 3.047 (q, J = 0.017, 1H), 2.405-2.355(m, 1H), 2.018-1.922 (m, 3H), 1.827-1.766 (m, 3H), 1.666 (sextet, J = 0.016, 1H) MS (m/z): 444.5
287		MS (m/z): 529.6

288		MS (m/z): 458.5
289		MS (m/z): 558.6
290		MS (m/z): 516.6
291		MS (m/z): 501.6
292		MS (m/z): 515.6
293		MS (m/z): 543.7
294		MS (m/z): 557.6
295		MS (m/z): 571.7
296		MS (m/z): 514.6

297		1H NMR 400 MHz (DMSO-d6) 8.472 (s, 1H), 8.165 (d, J = 0.019, 1H), 8.003-7.976 (m, 2H), 7.888 (brs, 1H), 7.630-7.600 (m, 2H), 7.376 (q, J = 0.019, 1H), 7.148 (d, J = 0.019, 2H), 7.010 (t, J = 0.019, 2H), 5.496 (brs, 2H), 5.160 (d, J = 0.017, 1H), 4.148 (d, J = 0.007, 2H), 7.007-3.953 (m, 1H), 3.806 (d, J = 0.022, 3H), 3.674-3.582 (m, 4H), 2.031-1.958 (m, 2H), 1.854-1.819 (m, 1H) MS (m/z): 538.6

Assays

Preparation of compound dilutions

[000438] Test compounds were dissolved in DMSO (10 mM) and transferred into 1.4mL flat bottom or V-shaped Matrix tubes carrying a unique 2D matrix chip by individual compound hubs. The numbers of these chips were distinctively linked to the individual compound identification numbers. The stock solutions were stored at –20°C if not used immediately. For the test procedure the vials were defrosted and identified by a scanner whereby a working sheet is generated that guides the subsequent working steps.

[000439] Compound dilutions were made in 384 well plates. This format enabled the assay of maximally 28 individual test compounds at 12 concentrations (single points) including 2 reference compounds. The dilution protocol included the production of pre-dilution plates, master plates and assay plates:

Compound plates: 30 µL of individual compound (10 mM) DMSO solution including standard compound were transferred into columns 1 and 13 of a 384 well plate. 20 µL of DMSO were added to the rest of the wells and the compounds were serially diluted (1:3) by transferring 10 µL from a well in column 1 or 13 to the next well in column 2 or 14 respectively and successively with the help of a Minitrack robot.

Assay plates: Identical assay plates were then prepared by adding 50 nL each of compound dilutions of the compound plates into 384-well "assay plates". In the following the compounds were mixed with 50 µL of assays components (cells or enzyme) and tested for their inhibitory activity.

[000440] Compounds of Formula (I) were assayed to measure their capacity to inhibit TrkA, TrkB, and/or TrkC protein kinases. Other compounds of Formula (I) were assayed to measure their capacity to inhibit a kinase panel, including but not limited to Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK protein kinases.

Effect on proliferation of various kinases dependent cells

[000441] Compounds of Formula (I) were tested for their antiproliferative effect on Ba/F3 cells expressing either Tel-TrkA, Tel-TrkB or Tel-TrkC and an additional panel of 34 selected diverse kinases activated by fusion to the dimerizing partners Bcr or Tel (Abl, AlK, BMX, EphA3, EphB2, FGFR2, FGFR3, FGFR4, FGR, FLT1, FLT3, FLT4, FMS, IGF1R, InsR, JAK1, JAK2, JAK3, KDR, Kit, Lck, Lyn, MER, MET, PDGFRb, RET, RON, Ros-1, Src, Aurora, TIE2, TYK2, Tie1, ZAP70) . The antiproliferative effect of these compounds on the different cell lines and on the non transformed cells were tested at 12 different concentrations of 3-fold serially diluted compounds in 384 well plates as described above (in media lacking IL3). The IC_{50} values of the compounds the different cell lines were determined from dose response curves.

Upstate KinaseProfilerTM – Radio-enzymatic filter binding assay

[000442] Compounds of Formula (I) were assessed for their ability to inhibit individual members of a panel of kinases (a partial, non-limiting list of kinases includes: Abl, Aurora, cSrc, TPR-Met, Tie2, MET, FGFR3, Axl, Bmx, BTK, c-kit, CHK2, FLT3, MST2, p70S6K, PDGFR, PKB, PKCα, Raf, ROCK-II, Rsk1, SGK, TrkA, TrkB and TrkC, Ros, KDR, FMS, c-FMS, JAK2, JAK3, Lck, IGF-1R, ALK4, ALK5 and ALK kinases). The compounds were tested in duplicates at a final concentration of 10 μM following this generic protocol. Note that the kinase buffer composition and the substrates vary for the different kinases included in the "Upstate KinaseProfiler™" panel. Kinase buffer (2.5 μL, 10x - containing $MnCl_2$ when required), active kinase (0.001-0.01 Units; 2.5 μL), specific or Poly(Glu4-Tyr) peptide (5-500 μM or .01 mg/ml) in kinase buffer and kinase buffer (50 μM; 5 μL) were mixed in an eppendorf on ice. A Mg/ATP mix (10 μL; 67.5 (or 33.75) mM $MgCl_2$, 450 (or 225) μM ATP and 1 μCi/μl [γ-^{32}P]-ATP (3000Ci/mmol)) is added and the reaction is incubated at about 30 °C for about 10 minutes. The reaction mixture is spotted (20 μL) onto a 2cm x 2cm P81 (phosphocellulose, for positively charged peptide substrates) or Whatman No. 1 (for Poly (Glu4-Tyr) peptide substrate) paper square. The assay squares were washed 4 times, for 5 minutes each, with 0.75% phosphoric acid and washed once with acetone for 5 minutes. The assay squares were transferred to a scintillation vial, 5 ml scintillation cocktail were added and ^{32}P incorporation (cpm) to the peptide substrate is quantified with a Beckman scintillation counter. Percentage inhibition is calculated for each reaction.

Inhibition of cellular TrkA, TrkB and TrkC dependent proliferation

[000443] Compounds of Formula (I) were assayed to measure their capacity to selectively inhibit cell proliferation of Ba/F3 cells expressing activated TrkA, TrkB or TrkC through fusion to the dimerization domain of Tel (ETV6) transcription factor as well as Ba/F3 cells co-expressing full length rTrkA and mNGF compared with parental BaF3 cells.

[000444] The cell line used is the luciferase expressing Ba/F3 murine hematopoietic progenitor cell line

transformed with human Tel-TrkA, Tel-TrkB or Tel-TrkC cDNAs (Ba/F3 EN A/B/C). These cells maintained in RPMI/10% fetal bovine serum (RPMI/FCS) supplemented with penicillin 50 mg/mL, streptomycin 50 mg/mL and L-glutamine 200 mM. Untransformed Ba/F3 cells were similarly maintained with the addition 5ng/ml of murine recombinant IL3. 50 µl of a Ba/F3 or Ba/F3 EN A/B/C cell suspension were plated in Greiner 384 well microplates (white) at a density of 2000 cells per well. 50nl of serially diluted test compound (10-0.0001 mM in DMSO solution) is added to each well. The cells were incubated for 48 hours at 37 °C, 5% CO_2. 25µl of Bright glo® (Promega) luciferase substrate is added to each well. The emited luminiscence is quantified using the ACQUEST™ luminescence system (Molecular Devices). IC_{50} values were calculated by linear regression analysis of the percentage inhibition of each compound at 12 concentrations.

Inhibition of cellular Anaplastic Lymphoma Kinase (ALK) kinase activity

[000445] The inhibition of ALK tyrosine kinase activity is demonstrated using known methods, for example using the recombinant kinase domain of the ALK in analogy to the VEGF-R kinase assay described in J. Wood et al. Cancer Res. 60, 2178-2189 (2000). In general, *in vitro* enzyme assays using GST-ALK protein tyrosine kinase were performed in 96-well plates as a filter binding assay in 20 mM Tris HCl, pH = 7.5, 3 mM $MgCl_2$, 10 mM $MnCl_2$, 1 mM DTT, 0.1 µCi/assay (=30 µl) [γ-^{33}P]-ATP, 2 µM ATP, 3 µg/mL poly (Glu, Tyr 4:1) Poly-EY (Sigma P-0275), 1 % DMSO, 25 ng ALK enzyme. Assays were incubated for 10 min at ambient temperature. Reactions were terminated by adding 50 µl of 125 mM EDTA, and the reaction mixture is transferred onto a MAIP Multiscreen plate (Millipore, Bedford, MA, USA), previously wet with methanol, and rehydrated for 5 minutes with H_2O. Following washing (0.5 % H_3PO_4), plates were counted in a liquid scintillation counter. IC_{50} values were calculated by linear regression analysis of the percentage inhibition.

[000446] Compounds of Formula (I) potently inhibit the growth of human NPM-ALK overexpressing murine BaF3 cells. The expression of NPM-ALK is achieved by transfecting the BaF3 cell line with an expression vector pCIneo™ (Promega Corp., Madison WI, USA) coding for NPM-ALK and subsequent selection of G418 resistant cells. Non-transfected BaF3 cells depend on IL-3 for cell survival. In contrast, NPM-ALK expressing BaF3 cells (named BaF3-NPM-ALK hereinafter) can proliferate in the absence of IL-3 because they obtain proliferative signal through NPM-ALK kinase. Putative inhibitors of the NPM-ALK kinase therefore abolish the growth signal and results in antiproliferative activity. The antiproliferative activity of putative inhibitors of the NPM-ALK kinase can however be overcome by addition of IL-3, which provides growth signals through an NPM-ALK independent mechanism. An analogous cell system using FLT3 kinase has also been described (see, E Weisberg et al. Cancer Cell; 1, 433-443 (2002)).

[000447] The inhibitory activity of the compounds of Formula (I) is determined as follows. In general,

BaF3-NPM-ALK cells (15,000/microtitre plate well) were transferred to 96-well microtitre plates. Test compounds dissolved in dimethyl sulfoxide (DMSO) were added in a series of concentrations (dilution series) in such a manner that the final concentration of DMSO is not greater than 1 % (v/v). After the addition, the plates were incubated for two days during which the control cultures without test compound were able to undergo two cell-division cycles. The growth of the BaF3-NPM-ALK cells is measured by means of YOPRO™ staining [T Idziorek et al. J. Immunol. Methods; 185: 249-258 (1995)]: 25 µl of lysis buffer comprising 20 mM sodium citrate, pH 4.0, 26.8 mM sodium chloride, 0.4 % NP40, 20 mM EDTA and 20 mM is added to each well. Cell lysis is completed within 60 minutes at room temperature and total amount of YOPRO™ bound to DNA is determined by measurement using the Cytofluor II 96-well reader (PerSeptive Biosystems) with the following settings: Excitation (nm) 485/20 and Emission (nm) 530/25.

[000448] IC_{50} values were determined by a computer-aided system using the formula: $IC_{50} = [(ABS_{test}-ABS_{start})/(ABS_{control}-ABS_{start})] \times 100$. (ABS = absorption). The IC_{50} value is given as the concentration of the test compound in question that results in a cell count that is 50 % lower than that obtained using the control without inhibitor.

[000449] The antiproliferative action of compounds of Formula (I) were also determined in the human KARPAS-299 lymphoma cell line (DSMZ Deutsche Sammiung von Mikroorganismen und Zelikulturen GmbH, Braunschweig, Germany, described in WG Dirks et al. Int. J. Cancer 100, 49-56 (2002)) using the same methodology described above for the BaF3-NPM-ALK cell line. In some embodiments, compounds of Formula (I) exhibit inhibitory activity with an IC_{50} in the range from approximately 0.01 to 1 µM. The action of compounds of Formula (I) on autophosphorylation of the ALK is determined in the human KARPAS-299 lymphoma cell line by means of an immunoblot as described in WG Dirks et al. Int. J. Cancer 100, 49-56 (2002).

Inhibition of cellular KDR dependent proliferation

[000450] Compounds of Formula (I) were assayed to measure their capacity to selectively inhibit cell proliferation of Ba/F3 cells expressing activated KDR through fusion to the dimerization domain of Tel (ETV6) transcription factor compared with parental BaF3 cells.

[000451] Luciferase expressing Ba/F3 murine pro-B cells were transformed with Tel-KDR. Cells were maintained in RPMI/10% fetal calf serum (RPMI/FCS) supplemented with penicillin 50 µg/mL, streptomycin 50 µg/mL and L-glutamine 200 mM. Untransformed Ba/F3 cells were similarly maintained with the addition of murine recombinant IL3. Cells were dispensed into 384-well format plate at 5000 cell/well in 50 µL of culture medium. Compounds of Formula (I) were dissolved and diluted in dimethylsufoxide (DMSO). Twelve points 1:3 serial dilutions were made into DMSO to create concentrations gradient ranging from 10 mM to 0.05 µM. Cells were added with 50 nL of diluted compounds and incubated for 48 hours in cell culture incubator. Luminiscent signal is measured following the addition of Bright glo® (Promega) luciferase substrate. IC_{50} values were calculated by linear regression

analysis of the percentage inhibition of each compound at 12 concentrations.

FLT-3 (Enzymatic Assay)

[000452] Kinase activity assay with purified FLT-3 (Upstate) is carried out in a final volume of 10 µL containing 0.25 µg/mL of enzyme in kinase buffer (30 mM Tris-HCl pH7.5, 15 mM $MgCl_2$, 4.5 mM $MnCl_2$, 15 µM Na_3VO_4 and 50 µg/mL BSA), and substrates (5 µg/mL biotin-poly-EY(Glu, Tyr) (CIS-US, Inc.) and 3µM ATP). Two solutions were made: the first solution of 5 µl contains the FLT-3 enzyme in kinase buffer is first dispensed into 384-well format ProxiPlate® (Perkin-Elmer) followed by adding 50 nL of compounds dissolved in DMSO, then 5 µl of second solution contains the substrate (poly-EY) and ATP in kinase buffer is added to each wells. The reactions were incubated at room temperature for one hour, stopped by adding 10 µL of HTRF detection mixture, which contains 30 mM Tris-HCl pH 7.5, 0.5 M KF, 50 mM ETDA, 0.2 mg/mL BSA, 15 µg/mL streptavidin-XL665 (CIS-US, Inc.) and 150 ng/mL cryptate conjugated anti-phosphotyrosine antibody (CIS-US, Inc.). After one hour of room temperature incubation to allow for streptavidin-biotin interaction, time resolved florescent signals were read on Analyst GT (Molecular Devices Corp.). IC_{50} values were calculated by linear regression analysis of the percentage inhibition of each compound at 12 concentrations (1:3 dilution from 50 µM to 0.28 nM). In this assay, compounds of Formula (I) have an IC_{50} in the range of 10 nM to 2 µM.

FLT-3 (Cellular Assay)

[000453] Compounds of Formula (I) were tested for their ability to inhibit transformed Ba/F3-FLT3-ITD cell proliferation, which is depended on FLT-3 cellular kinase activity. Ba/F3-FLT3- ITD were cultured up to 800,000 cells/mL in suspension, with RPMI 1640 supplemented with 10% fetal bovine serum as the culture medium. Cells were dispensed into 384-well format plate at 5000 cell/well in 50 µL culture medium. Compounds of Formula (I) were dissolved and diluted in dimethylsulfoxide (DMSO). Twelve points 1:3 serial dilutions were made into DMSO to create concentrations gradient ranging typically from 10 mM to 0.05 µM. Cells were added with 50 nL of diluted compounds and incubated for 48 hours in cell culture incubator. AlamarBlue® (TREK Diagnostic Systems), which can be used to monitor the reducing environment created by proliferating cells, were added to cells at final concentration of 10%. After additional four hours of incubation in a 37 °C cell culture incubator, fluorescence signals from reduced AlamarBlue® (Excitation at 530 nm, Emission at 580 nm) were quantified on Analyst GT (Molecular Devices Corp.). IC_{50} values were calculated by linear regression analysis of the percentage inhibition of each compound at 12 concentrations

cKit – Proliferation Assay

[000454] Compounds were tested for their ability to inhibit the proliferation of wt Ba/F3 cells and Ba/F3 cells transformed with Tel c-kit fused tyrosine kinases. Untransformed Ba/F3 cells were maintained in media containing recombinant IL3. Cells were plated into 384 well TC plates at 5,000 cells in 50ul media

per well and test compound at 0.06 nM to 10 μM is added. The cells were then incubated for 48 hours at 37 °C, 5% CO2. After incubating the cells, 25 μL of BRIGHT GLO® (Promega) is added to each well following manufacturer's instructions and the plates were read using Analyst GT – Luminescence mode – 50000 integration time in RLU. IC50 values, the concentration of compound required for 50% inhibition, were determined from a dose response curve.

cKit – Mo7e Assay

[000455] The compounds described herein were tested for inhibition of SCF dependent proliferation using Mo7e cells which endogenously express c-kit in a 96 well format. Briefly, two-fold serially diluted test compounds (Cmax=10μM) were evaluated for their antiproliferative activity of Mo7e cells stimulated with human recombinant SCF. After 48 hours of incubation at 37°C, cell viability is measured by using a MTT colorimetric assay from Promega.

Description of biochemical assay for DNA-PK:

[000456] The assay is conducted using the kit V7870 from Promega (SignaTECT® DNA-Dependent Protein Kinase Syste, comprises DNA-PK, biotinylated peptide substrate end further ingredients, Promega, Madison, Wisconsin, USA), that quantitates DNA-dependent protein kinase activity, both in purified enzyme preparations and in cell nuclear extracts. DNA-PK is a nuclear serine/threonine protein kinase that requires double-stranded DNA (dsDNA) for activity. The binding of dsDNA to the enzyme results in the formation of the active enzyme and also brings the substrate closer to the enzyme, allowing the phosphorylation reaction to proceed.

[000457] DNA-PK X5 reaction buffer (250 mM HEPES, 500 mM KCl, 50 mM $MgCl_2$, 1 mM EGTA, 0.5 mM EDTA, 5 mM DTT, pH to 7.5 with KOH) is diluted 1/5 in deionised water and BSA (stock = 10 mg/ml) is added to a final concentration of 0.1 mg/ml.

[000458] The activation buffer is made from 100 μg/ml of calf thymus DNA in control buffer (10 mM Tris-HCl (pH 7.4), 1 mM EDTA (pH 8.0)). Per tube, the reaction mix is composed of: 2.5 μl of activation or control buffers, 5 μl of X5 reaction buffer, 2.5 μl of p53-derived biotinylated peptide substrate (stock= 4mM), 0.2 μl of BSA (stock at 10 mg/ml) and 5 μl of [γ-^{32}P] ATP (5 μl of 0.5 mM cold ATP + 0.05 μl of Redivue [γ-^{32}P] ATP = Amersham AA0068-250 μCi, 3000Ci/mmol, 10 μCi/μl (now GE Gealthcare Biosciences AB, Uppsala, Sweden).

[000459] The DNA-PK enzyme (Promega V5811, concentration=100 U/μL) is diluted 1/10 in X1 reaction buffer and kept on ice until imminent use. 10.8 μl of the diluted enzyme is incubated with 1.2 μl of 100 μM compounds (diluted 1/100 in water from 10 mM stock in neat DMSO) for 10 minutes, at room temperature. During that time, 15.2 μl of the reaction mix is added to screw-capped tubes, behind Perspex glass. 9.8 μl of the enzyme is then transferred to the tubes containing the reaction mix and after 5 minutes incubation, at 30°C, the reaction is stopped by adding 12.5 μl of termination buffer (7.5 M guanidine hydrochloride).

[000460] After mixing well, a 10 µl aliquot of each tube is spotted onto a SAM2® biotin capture membrane (Promega, Madison, Wisconsin, USA), which is left to dry for a few minutes. The membrane is then washed extensively to remove the excess free [γ-^{32}P] ATP and nonbiotiny-ated proteins: once for 30 seconds in 200 ml of 2M NaCl, 3 times for 2 minutes each in 200 ml of 2M NaCl, 4 times for 2 minutes each in 2M NaCl in 1% H_3PO_4 and twice for 30 seconds each in 100 ml of deionised water. The membrane is subsequently left to air-dry at room temperature for 30-60 minutes.

[000461] Each membrane square is separated using forceps and scissors and placed into a scintillation vial, after which 8 ml of scintillation liquid (Flo-Scint 6013547 from Perkin-Elmer) is added. The amount of ^{32}P incorporated into the DNA-PK biotinylated peptide substrate is then determined by liquid scintillation counting.

Protocol for the detection of phospho-PKB in U87MG cells by Elisa:

[000462] The efficacy of the compounds of Formula (I) in blocking the activation of the PI3K/PKB pathway can be demonstrated in cellular settings as follows: U87MG cells (human glioblastoma, ATCC No. HTB-14) were trypsinized, counted in a CASY cell counter (Schärffe systems, Göttingen, Germany), diluted in fresh complete DMEM high glucose medium to load, per well , 150 µL cell suspension containing 4 x 10^4 cells, and test plates incubated for 18 hours. In parallel, 50 µL of coating antibody, at the desired concentration in PBS/O is loaded in each well of the ELISA plates, and plates were kept for 2 hours at room temperature. This ELISA assays is performed in black flat-bottom 96-well plates (Microtest™, Falcon Becton-Dickinson, Ref: 353941) sealed with Plate Sealers (Costar-Corning, Ref: 3095). Medium in plates is discarded and replaced by complete DMEM high glucose medium containing either 0.1% DMSO or 0.1% inhibitor at titers (7) between 10 mM and 0.156 mM in DMSO. After 30 minutes of contact, the medium is quickly removed by aspiration, plates were then placed on ice and immediately cells lyzed with 70 µL of Lysis buffer. In parallel, the 96 wells plates prepared with the coating antibody (1/250 diluted (in PBS/O) Anti-Akt1 C-20, goat, Santa-Cruz-1618, Santa Cruz Biotechnology, Inc., Santa Cruz, California, USA) were washed 3 times for 1 minute with PBS/O containing 0.05% Tween 20 and 0.1% Top-Block® (derivative of gelatine that blocks unspecific binding sites on surfaces; Sigma-Aldrich, Fluka, Buchs, Switzerland, Ref.: 37766), and remaining protein binding sites blocked to prevent non-specific interactions with 200 µL of PBS containing 3% Top Block®, for 2 hours at room temperature. Well content is replaced with 50 µL of samples from treated cells, and plates were incubated for 3 hours at 4°C. The ELISA assays were always done in parallel with the following controls, in 6 replicates: U87MG (untreated control) or Lysis buffer alone (LB). After 3 x 15 minutes washes, all wells received 50 µL of the secondary antibody (1/250 diluted (in 3% top block) Anti-S473P-PKB, rabbit, Cell Signaling-9271, Cell Signaling Technologies, Inc., Danvers, Massachusetts, USA)), and were incubated for 16 hours at 4°C. After three washes, plates were incubated with the third and conjugated antibody (1/1000 diluted (in 3% top block) anti rabbit (HRP) Jackson Immuno Research 111-035-144) for 2 hours at room temperature. Finally, the

immune-complexes were washed 2 times 15 seconds with PBS/O/ tween20 /top block, 1 time with 200 µL of water and finally 200 µL of water were left in each test well before a 45 minute incubation in darkness. The plates were then assayed with (SuperSignal® ELISA pico Chemiluminescent substrate, Pierce, Ref: 27070, Pierce Biotechnology, Inc., Rockford, Illinois, USA). 100 µL of substrate were added, and plates shacked for 1 minute. The luminescence is read immediately on a Top-Count NXT (Packard Bioscience) luminometer.

[000463] There were also experiments that demonstrated the antitumor activity of compounds of the Formula (I) *in vivo*. For example, female Harlan (Indianapolis, Indiana, USA) athymic nu/nu mice with s.c. transplanted human glioblastoms U87MG tumors can be used to determine the anti-tumor activity of PI3 kinase inhibitors. On day 0, with the animals under peroral Forene® (1-chloro-2,2,2-trifluoroethyldifluormethylether, Abbot, Wiesbaden, Germany) narcosis, a tumor fragment of approximately 25 mg is placed under the skin on the animals' left flank and the small incised wound is closed by means of suture clips. When tumors reach a volume of 100 mm^3, the mice were divided at random into groups of 6-8 animals and treatment commences. The treatment is carried out for a 2-3 weeks period with peroral, intravenous or intra-peritoneal administration once daily (or less frequently) of a compound of formula (I) in a suitable vehicle at defined doses. The tumors were measured twice a week with a slide gauge and the volume of the tumors is calculated.

[000464] As an alternative to cell line U87MG, other cell lines may also be used in the same manner, for example, the MDA-MB 468 breast adenocarcinoma cell line (ATCC No. HTB 132; see also In Vitro 14, 911-15 [1978]); the MDA-MB 231 breast carcinoma cell line (ATCC No. HTB-26; see also In Vitro 12, 331 [1976]); the MDA-MB 453 breast carcinoma cell line (ATCC No.HTB-131); the Colo 205 colon carcinoma cell line (ATCC No. CCL 222; see also Cancer Res. 38, 1345-55 [1978]); the DU145 prostate carcinoma cell line DU 145 (ATCC No. HTB 81; see also Cancer Res. 37, 4049-58 [1978]); the PC-3 prostate carcinoma cell line PC-3 (especially preferred; ATCC No. CRL 1435; see also Cancer Res. 40, 524-34 [1980]) and the PC-3M prostate carcinoma cell line; the A549 human lung adenocarcinoma (ATCC No. CCL 185; see also Int. J. Cancer 17, 62-70 [1976]); the NCI-H596 cell line (ATCC No. HTB 178; see also Science 246, 491-4 [1989]), and the pancreatic cancer cell line SUIT-2 (see Tomioka et al., Cancer Res. 61, 7518-24 [2001]).

Kinase Activity of ALK5

[000465] The kinase activity of ALK5 is assessed by measuring radiolabelled phosphate [33P] incorporation in to the generic substrate, casein. The kinase domain of human ALK5 (amino acids 200-503) is fused to an N-terminal histidine tag. The kinase activity of ALK5 is rendered constitutive via point mutation at amino acid 204 (threonine to aspartate modification, ALK5 T204D) and the kinase construct is engineered to be expressed from a baculovirus expression construct in insect cells. The purified, recombinantly-expressed histidine-tagged ALK5 T204D protein is dissolved at 5.4 mg/ml in 50 mM Tris-

HCl pH 8.0, 150 mM NaCl, 5 mM DTT. ALK5 T204D is dissolved to 2.5 µg/ml in assay buffer (Assay buffer: 20 mM Tris-HCl pH 7.4, 10 mM $MgCl_2$, 2 mM $MnCl_2$) on the day of use.

[000466] Test compounds and reference compounds were dissolved in assay buffer without DTT containing 5% (v/v) DMSO. Stock solutions of test and reference compounds were diluted in assay buffer with DTT (1.25 mM) containing 4.5% (v/v) DMSO. 10 µl of test or reference compound were added to the appropriate wells of 96 well U-bottomed plate. Total enzyme activity is determined by measuring ALK5 T204D activity in the absence of ALK5 kinase inhibitor reference compounds. Non-specific binding (NSB) is determined by measuring the activity of ALK5 T204D in the presence of ALK5 kinase inhibitor reference compounds. 10 µl of dephosphorylated casein stock solution (dephosphorylated casein is dissolved in ddH_2O at 20 mg/ml) is added per well (200 µg/well final assay concentration). 20 µl of ALK5 T204D (2.5 µg/ml solution) is added per well (50 ng/well final assay concentration). The plates were left to incubate at room temperature for 10 minutes. 10 µl of ATP mix is added to the well to initiate the reaction (0.66 nM [^{33}P]ATP/1 µM unlabelled ATP/well final assay concentration). The ATP mix is prepared as follows, unlabelled ATP (3 mM) is dissolved in ddH_2O and pH adjusted to 7.4. The stock concentration of [^{33}P]ATP is 10 µCi/µl. The appropriate volume of [^{33}P]ATP is added to unlabelled ATP solution such that the final assay concentration per well is 0.1 µCi. Following addition of the ATP mix, the plates were incubated at room temperature for 50 minutes. The kinase reaction is terminated by the addition of 50 µL Stop Buffer (20 mM Tris-HCl pH 7.4, 10 mM EDTA). 75 µl/well from the reaction plate is transferred to a Multiscreen-IP plate (MultiScreen-IP plates were prepared by added 50 µL of 70% (v/v) ethanol per well and incubated for 5 minutes at room temperature. The ethanol is removed by aspiration via a MultiScreen HTS Vaccum Manifold unit (Millipore, Cat no: MSVMHT500). The plates were washed twice by adding 200 µl/well ddH_2O). The MultiScreen-IP plate is incubated at room temperature for 30 minutes to allowing binding of casein to the plate. The MultiScreen-IP plates were washed three times by adding 200 µl/well 100 mM phosphoric acid solution and the gasket is carefully removed from the back of the MultiScreen-IP plate and the plate dried in the oven for 30 minutes. The MultiScreen-IP plate is backsealed, 50 µL of Microscint^{TM}20 is added, then the plates were topsealed and radiolabelled casein detected and quantified on a TopCount^{TM} plate-reader using the ^{33}P scintillation protocol.

JAK/TYK-kinase family profiling assays

[000467] The efficacy of the compounds of Formula (I) as inhibitors of JAK/TYK kinase activity can be demonstrated as follows: All four kinases of the JAK/TYK-kinase family were used as purified recombinant GST-fusion proteins, containing the active kinase domains. GST-JAK1(866-1154), GST-JAK3(811-1124), and GST-TYK2(888-1187) were expressed and purified by affinity chromatography. GST-JAK2(808-1132) is purchased from Invitrogen (Carlsbad, USA, #4288). The kinase assays were based on the Caliper mobility shift assay using the LabChip 3000 systems. This technology is similar to capillary electrophoresis and uses charge driven separation of substrate and product in a microfluidic chip. All kinase

reactions were performed in 384 well microtiter plates in a total reaction volume of 18 µl. The assay plates were prepared with 0.1 µl per well of test compound in the appropriate test concentration, as described under the section "preparation of compound dilutions". The reactions were started by combining 9 µl of substrate mix (consisting of peptide and ATP) with 9 µl of kinase dilution. The reactions were incubated for 60 minutes at 30°C and stopped by adding 70 µl of stop buffer (100 mM Hepes, 5% DMSO, 0.1% Coating reagent, 10 mM EDTA, 0.015% Brij 35). Fluorescently labeled synthetic peptides were used as substrates in all reactions. A peptide derived from the sequence of IRS-1 (IRS-1 peptide, FITC-Ahx-KKSRGDYMTMQIG-NH2) is used for JAK1 and TYK2 and a peptide named JAK3tide (FITC-GGEEEEYFELVKKKK-NH2) for JAK2 and JAK3. Specific assay conditions are described in TableA:

TableA: Assay conditions of individual kinase assays

Kinase	JAK1	JAK2	JAK3	TYK2
Buffer	50 mM Hepes pH 7.5, 0.02% Tween 20, 1 mM DTT, 0.02% BSA, 12 mM MgCl2	50 mM Hepes pH 7.5, 0.02% Tween 20, 1 mM DTT, 0.02% BSA, 9 mM MgCl2	50 mM Hepes pH 7.5, 0.02% Tween 20, 1 mM DTT, 0.02% BSA, 1.5 mM $MgCl_2$	50 mM Hepes pH 7.5, 0.02% Tween 20, 1 mM DTT, 0.02% BSA, 9 mM MgCl2
DMSO	0.6 %	0.6 %	0.6 %	0.6 %
Kinase conc.	50 nM	1.8 nM	6 nM	40 nM
Substrate peptide conc.	5 µM	2 µM	2 µM	5 µM
ATP conc.	40 µM	20 µM	80 µM	30 µM

[000468] The terminated reactions were transferred to the Caliper LabChip 3000 reader and the turnover of each reaction is measured by determining the substrate/product ratio.

PI3-kinase profiling assays

[000469] The efficacy of the compounds of Formula (I) as PI3 kinase inhibitors is demonstrated as follows: The kinase reaction is performed in a final volume of 50 µL per well of a half area COSTAR, 96 well plate. The final concentrations of ATP and phosphatidyl inositol in the assay were 5 µM and 6 µg/mL respectively. The reaction is started by the addition of PI3 kinase p110β. The components of the assay were added per well as follows:

- 10 µL test compound in 5% DMSO per well in columns 2-1.
- Total activity is determined by addition 10 µL of 5% vol/vol DMSO in the first 4 wells of column 1 and the last 4 wells of column 12.

- The background is determined by addition of 10 μM control compound to the last 4 wells of column 1 and the first 4 wells of column 12.
- 2 mL 'Assay mix' were prepared per plate:
    - 1.912 mL of HEPES assay buffer
    - 8.33 μL of 3 mM stock of ATP giving a final concentration of 5 μM per well
    - 1 μL of [^{33}P]ATP on the activity date giving 0.05 μCi per well
    - 30 μL of 1 mg/mL PI stock giving a final concentration of 6 μg/mL per well
    - 5 μL of 1 M stock $MgCl_2$ giving a final concentration of 1 mM per well
- 20 μL of the assay mix were added per well.
- 2 mL 'Enzyme mix' were prepared per plate (x* μL PI3 kinase p110β in 2 mL of kinase buffer). The 'Enzyme mix' is kept on ice during addition to the assay plates.
- 20 μL 'Enzyme mix' were added/well to start the reaction.
- The plate is then incubated at room temperature for 90 minutes.
- The reaction is terminated by the addition of 50 μL WGA-SPA bead (wheat germ agglutinin-coated Scintillation Proximity Assay beads) suspension per well.
- The assay plate is sealed using TopSeal-S heat seal for polystyrene microplates, PerkinElmer LAS (Deutschland) GmbH, Rodgau, Germany) and incubated at room temperature for at least 60 minutes.
- The assay plate is then centrifuged at 1500 rpm for 2 minutes using the Jouan bench top centrifuge (Jouan Inc., Nantes, France).
- The assay plate is counted using a Packard TopCount, each well being counted for 20 seconds.
- The volume of enzyme is dependent on the enzymatic activity of the batch in use.

[000470] Some of the compounds show a certain level of selectivity against the different paralogs PI3K alpha, beta, gamma and delta.

Certain Assay Results

[000471] Various compounds of Formula (I) in free form or in pharmaceutically acceptable salt form, exhibit pharmacological properties, for example, as indicated by the *in vitro* and *in vivo* tests described in this application. The IC_{50} value in those experiments is given as that concentration of the test compound in question that results in a cell count that is 50 % lower than that obtained using the control without inhibitor. In certain examples compounds of Formula (I) have IC_{50} values from 1 nM to 200 μM. In some examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 100 μM.

In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 50 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 25 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 20 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 15 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 10 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 5 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 2 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 1 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 0.8 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 0.6 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 0.4 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 0.2 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 0.1 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 0.08 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 0.06 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 0.04 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 0.02 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.001 μM to 0.01 μM.

[000472] In some examples, compounds of Formula (I) have IC_{50} values from 0.01 μM to 5 μM. In other examples, compounds of Formula (I) have IC_{50} values from 0.01 μM to 1 μM. In yet other examples, compounds of Formula (I) have IC_{50} values of less than 1 nM. In certain embodiments, compounds of Formula (I) exhibit a percentage inhibition of greater than 50%, or in other embodiments compounds of Formula (I) exhibit a percentage inhibition greater than about 70%, against one or more of the following kinases at 10 μM: Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and/or ALK kinases.

[000473] By way of example only, the compound (R)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)piperidin-4-ol (see Example 16-4) has an IC_{50} of 4.41 μM, 0.0052 μM, 0.012 μM, 0.013 μM, in BaF_3, BaF_3/Tel-TrkA, BaF_3/Tel-TrkB and BaF_3/TrkA-NFG CTG cellular assays, respectively.

[000474] By way of example only, the compound (R)-1-(4-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)pyrrolidin-3-ol (see Example 14-4) has an IC_{50} of 4.07 μM, 0.0022 μM, 0.0033 μM, 0.0042 μM, in BaF_3, BaF_3/Tel-TrkA, BaF_3/Tel-TrkB and BaF_3/TrkA-NFG CTG cellular assays, respectively.

[000475] By way of example only, the IC_{50} for TrkA, TrkB, TrkC inhibition by certain compounds of

Formula (I) are listed in Table 8 below. The identification of each compound in Table 8 corresponds to the Table Number where the compound is listed above and the respective compound number.

Table 8

Table No./Compound Number	Ba/F3 IC 50 (μM)	Ba/F3 Tel-TrkA IC 50 (μM)	Ba/F3 Tel-TrkB IC 50 (μM)	Ba/F3 Tel-TrkC IC 50 (μM)	BaF3 TRKA-NGF CTG IC 50 (μM)	KM12 luc IC 50 (μM)
Table 1-Compound 1	15.95	0.21	0.15	0.069	0.68	0.23
Table 1-Compound 3	>10	0.028	0.022	0.018	0.45	0.037
Table 1-Compound 4	---	1.60	0.79	---	---	---
Table 1-Compound 5	>10	5.67	4.17	2.61	3.58	2.29
Table 2-Compound 1	>9.69	0.013	0.0055	---	0.029	0.0070
Table 2-Compound 4	>10	0.0086	0.0058	---	0.017	0.0083
Table 2-Compound 6	>10	0.058	0.044	---	0.078	0.056
Table 2-Compound 7	>10	0.083	0.23	---	0.55	0.14
Table 2-Compound 8	>10	0.0016	0.0022	---	0.029	0.0052
Table 2-Compound 10	>10	0.0069	0.0062	---	0.0088	---
Table 2-Compound 16	>7.67	0.10	0.12	---	0.14	---
Table 2-Compound 18	>10	0.036	0.036	---	0.056	0.022
Table 2-Compound 19	5.05	2.17	1.70	---	1.42	---
Table 2-Compound 20	>10	0.39	0.39	---	0.28	---
Table 2-Compound 23	>10	0.01	0.024	---	0.012	---
Table 3-Compound 1	>10	2.31	0.47	0.24	1.73	0.19
Table 3-Compound	>10	1.33	0.95	0.21	0.62	0.90
Table 3-Compound 6	>10	0.36	0.76	0.18	0.54	0.38
Table 3-Compound 7	5.03	0.035	0.052	0.020	0.027	0.023
Table 3-Compound 10	>10	0.20	0.10	0.040	0.18	0.094

Table 3-Compound 11	>10	0.087	0.056	0.017	0.074	0.036
Table 3-Compound 18	7.23	0.013	0.010	0.0014	0.020	0.024
Table 3-Compound 19	>10	1.02	0.54	---	0.37	---
Table 3-Compound 26	>10	1.02	0.54	---	0.37	---
Table 3-Compound 27	>10	0.14	0.093	---	0.32	---
Table 3-Compound 30	>10	1.10	1.06	---	1.34	---
Table 3-Compound 34	>10	1.20	0.40	0.13	0.50	0.010
Table 3-Compound 41	0.2	0.20	0.21	---	0.11	---
Table 3-Compound 44	>10	1.12	1.14	----	1.20	---
Table 3-Compound 45	8.059	1.02	0.79	---	1.02	---
Table 3-Compound 52	>10	0.012	0.0077	0.004	0.022	0.0065
Table 3-Compound 54	>10	0.086	0.041	0.017	0.111	0.094
Table 3-Compound 58	7.65	0.044	0.049	0.014	0.108	0.034
Table 3-Compound 91	8.409	0.298	0.129	0.033	0.72	0.084
Table 4-Compound 5	>10	0.0007	0.0004	---	0.0022	0.0012
Table 4-Compound 14	5.716	0.021	0.0149	---	0.0452	0.0308
Table 4-Compound 16	>10	0.0068	0.0015	---	0.0052	0.0022
Table 4-Compound 25	7.502	0.010	0.0071	---	0.028	---
Table 4-Compound 32	4.989	0.0014	0.0015	---	0.0026	---
Table 5-Compound 1	7.658	0.051	0.038	0.021	0.043	0.0092
Table 5-Compound 2	6.174	0.026	0.015	0.0084	0.049	0.029
Table 5-Compound 4	5.36	0.166	0.060	0.032	0.203	0.089
Table 5-Compound 13	4.837	0.0035	0.035	0.0017	0.0053	0.0075
Table 5-Compound 17	>10	0.0064	0.015	0.0031	0.034	0.0088
Table 5-Compound 22	2.249	0.132	0.088	0.027	0.316	0.099

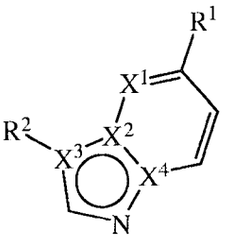
Table 5-Compound 23	3.713	0.136	0.074	0.016	0.111	0.109
Table 6-Compound 1	4.129	1.63	1.175	0.334	1.496	1.377
Table 6-Compound 3	>10	0.0015	0.0018	---	0.018	0.0072
Table 7-Compound 1	>10	0.017	0.017	---	0.030	0.0076
Table 7-Compound 2	>10	0.018	0.013	---	0.031	0.026
Table 7-Compound 3	3.866	0.0069	0.0066	---	0.019	0.017
Table 7-Compound 5	4.82	0.0038	0.0062	---	0.0064	---
Table 7-Compound 6	>10	0.023	0.039	---	0.062	---
Table 7-Compound 8	1.57	0.0082	0.0088	---	0.0061	---
Table 7-Compound 9	>10	0.059	0.063	---	0.053	0.014
Table 7-Compound 10	>10	0.061	0.071	---	0.077	---
Table 7-Compound 12	>10	0.0061	0.0067	---	0.0081	0.0012
Table 7-Compound 17	>10	0.081	0.044	---	0.093	---
Table 7-Compound 18	>10	0.047	0.0048	---	0.064	---
Table 7-Compound 20	>10	0.0018	0.0016	---	0.0036	---
Table 7-Compound 21	>10	0.090	0.067	---	0.121	---
Table 7-Compound 22	>10	0.043	0.023	---	0.035	---
Table 7-Compound 26	>10	0.0077	0.0075	---	0.012	---
Table 7-Compound 54	>10	0.028	0.037	---	0.041	---
Table 7-Compound 57	6.895	0.020	0.020	---	0.020	---
Table 7-Compound 58	>10	0.115	0.15	---	0.21	---
Table 7-Compound 61	>10	0.0081	0.0079	---	0.0098	0.0040
Table 7-Compound 82	0.397	0.0089	0.010	---	0.00512	---
Table 7-Compound 96	5.989	0.001	0.002		0.003	
Table 7-Compound 98	>11	0.006	0.009		0.013	
Table 7-Compound 100	4.378	0.002	0.002		0.003	
Table 7-Compound 115	4.842	0.014	0.014		0.016	
Table 7-	>9.10	0.003	0.003		0.008	0.003

Compound 116						
Table 7-Compound 119	>11	0.003	0.003		0.004	0.002
Table 7-Compound 121	>10	0.00334	0.00302	---	0.00488	---
Table 7-Compound 132	>11	0.002	0.002		0.004	
Table 7-Compound 136	4.324	0.013	0.024		0.039	
Table 7-Compound 143	>11	0.034	0.053		0.031	
Table 7-Compound 153	>11	0.346	0.244		0.698	
Table 7-Compound 158	>11	0.065	0.052		0.087	0.019
Table 7-Compound 171	>11	0.224	0.129		0.238	
Table 7-Compound 176	2.753	1.119	0.971		0.886	
Table 7-Compound 181	>11	0.007	0.008		0.014	
Table 7-Compound 185	>11	0.064	0.07		0.119	
Table 7-Compound 191	>9.56	0.014	0.012		0.016	
Table 7-Compound 201	>11	0.013	0.015		0.02	0.01
Table 7-Compound 217	>11	0.027	0.03		0.06	
Table 7-Compound 230	2.687	0.006	0.009		0.029	
Table 7-Compound 231	>11	0.023	0.028		0.054	
Table 7-Compound 238	>11	0.017	0.025		0.035	
Table 7-Compound 249	6.385	0.144	0.147		0.13	
Table 7-Compound 255	>11	0.009	0.017	0.003	0.009	0.006
Table 7-Compound 257	>11	0.13	0.289		0.101	

[000476] 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.

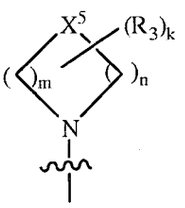
WE CLAIM:

1. A compound of Formula (I), pharmaceutically acceptable salt, pharmaceutically acceptable solvate thereof :



Formula (I)

wherein:

R^1 is  ;

wherein,

X^1, X^2, X^3 and X^4 are each independently CR^9, C or N, with the proviso that at least one of X^1, X^2 X^3 and X^4 is N and at most only two of X^1, X^2 X^3 and X^4 are N;

X^5 is $C(R^3)_2$, O, S, $S(O)_2$, S(O), or NR^3;

m is 1, 2, 3 or 4;

n is 0, 1, 2 or 3;

k is 0, 1, 2, 3, 4, 5 or 6;

each R^3 is independently selected from halogen, nitro, $-N(R^4)_2$, $-OR^9$, -CN, =O, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-C(O)OR^9$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, $-OC(O)R^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, C_1-C_8alkyl, C_6-C_{14}aryl, C_3-C_8cycloalkyl, halo-substituted-C_1-C_8alkyl, C_1-C_8alkoxy, hydroxyl-C_1-C_8alkyl, halo-substituted C_1-C_8alkoxy, C_2-C_{14}heterocycloalkyl and C_2-C_{13}heteroaryl, wherein the C_1-C_8alkyl, C_6-C_{14}aryl, C_3-C_8cycloalkyl, C_2-C_{14}heterocycloalkyl and C_2-C_{13}heteroaryl of R^3 are optionally substituted with 1 to 3 substituents independently

selected from halogen, amino, nitro, hydroxyl, cyano, -OR^9, –$C(O)N(R^4)_2$, –$N(R^4)C(O)OR^4$, –$N(R^4)C(O)R^4$, -$C(O)R^9$, -$C(O)OR^9$, -R^6, –OR^6, -L^1R^5, -L^1R^6, -Y^1R^5, -Y^1R^6, –$S(O)_2R^9$, –$S(O)_2N(R^4)_2$, –$NR^4S(O)_2$, -$OC(O)R^9$, -$(CH_2)_pOR^9$, -$L^1C(O)R^8$, -L^1R^8, -$C(O)R^9$, -$OC(O)R^9$, -$C(O)OR^9$, -$C(O)R^9$, -$N(R^9)_2$, –$C(O)N(R^4)_2$, –$N(R^4)C(O)R^4$, –$N(R^4)C(O)OR^4$, –$S(O)_2R^9$, –$S(O)_2N(R^4)_2$, –$NR^4S(O)_2$, C_1-C_8alkyl, C_1-C_8aminoalkyl, C_1-C_8alkoxy, C_1-C_8alkylthio, hydroxyl-C_1-C_8alkyl, halo-substituted-C_1-C_8alkyl, halo-substituted-C_1-C_8alkoxy, C_3-C_8cycloalkyl, C_2-C_{14}heterocycloalkyl, C_6-C_{14}aryl and C_2-C_{13}heteroaryl;

alternatively each R^3 is independently a C_1-C_8alkyl, wherein at least two R^3 together form a C_3-C_8cycloalkyl fused with a heterocycle and wherein each C_1-C_8alkyl of R^3 is optionally substituted with 1 to 3 substituents independently selected from halogen, amino, nitro, hydroxyl, cyano, -OR^9, C_1-C_8alkyl, C_1-C_8aminoalkyl, C_1-C_8alkoxy, C_1-C_8alkylthio, hydroxyl-C_1-C_8alkyl, halo-substituted-C_1-C_8alkyl, halo-substituted-C_1-C_8alkoxy, C_3-C_8cycloalkyl, C_2-C_{14}heterocycloalkyl, C_6-C_{14}aryl and C_2-C_{13}heteroaryl;

R^2 is C_6-C_{14}aryl, C_2-C_{13}heteroaryl or C_2-C_{14}heterocycloalkyl, wherein the C_6-C_{14}aryl, C_2-C_{13}heteroaryl or C_2-C_{14}heterocycloalkyl of R^2 are optionally substituted with 1 to 3 substituents independently selected from halogen, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, –$C(O)N(R^4)_2$, –$N(R^4)C(O)OR^4$, –$N(R^4)C(O)R^4$, -$C(O)R^9$, -OR^9, -$C(O)OR^9$, –$N(R^4)_2$, -R^6, –OR^6, -L^1R^5, -L^1R^6, -Y^1R^5, -Y^1R^6, –$S(O)_2R^9$, –$S(O)_2N(R^4)_2$, –$NR^4S(O)_2R^4$, -$OC(O)R^9$, C_1-C_8alkoxy, hydroxyl-C_1-C_8alkyl, halo-substituted C_1-C_8alkyl and halo-substituted C_1-C_8alkoxy;

each R^4 is independently selected from H, C_1-C_8 alkyl, -L^1R^5, -L^1R^6, -L^1R^8, C_2-C_{13}heteroaryl, C_6-C_{14}aryl, C_2-C_{14}heterocycloalkyl and C_3-C_8cycloalkyl, wherein the C_1-C_8alkyl, C_2-C_{13}heteroaryl and C_3-C_8cycloalkyl are optionally substituted with 1 to 3 substituents independently selected from halogen, deuterium, -CD_3, -$S(O)_2R^9$, -CN, C_1-C_8alkyl, -OR^9, -$N(R^9)_2$ and -$(CH_2)_pOR^9$;

L^1 is a bond, C_1-C_8alkylene, C_2-C_8alkenylene, -$O(CH_2)_p$-, -C(O)-, -$N(R^9)$-, $(CH_2)_pC(O)$-, -$C(O)(CH_2)_pO(CH_2)_p$- or -C(O)O-;

Y^1 is C_6-C_{14}arylene, C_2-C_{13}heteroarylene, C_3-C_8cycloalkylene, C_2-C_{14}heterocycloalkylene or C_1-C_8alkoxylene, each of which is optionally substituted with 1 to 3 substituents independently selected from halogen, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, –

$C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-OC(O)R^9$, C_1-C_8alkoxy, hydroxyl-C_1-C_8alkyl, halo-substituted C_1-C_8alkyl and halo-substituted C_1-C_8alkoxy;

R^5 is C_6-C_{14}aryl, C_2-C_{13}heteroaryl, C_2-C_{14}heterocycloalkyl, $-N(R^9)_2$, $-N(R^9)C(O)R^9$, $-C(O)N(R^9)_2$, $-(CH_2)_pOR^9$ or $-OR^9$.

R^6 is C_6-C_{14}aryl, C_2-C_{13}heteroaryl, C_2-C_{14}heterocycloalkyl, $-OCH(R^7)_2$, $-C(O)R^7$, C_1-C_8alkyl, or C_3-C_8cycloalkyl, wherein the C_1-C_8alkyl, C_3-C_8cycloalkyl, C_6-C_{14}aryl, C_2-C_{13}heteroaryl, and C_2-C_{14}heterocycloalkyl of R^6 are optionally substituted with 1 to 3 substituents independently selected from halogen, $-CN$, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^8$, $OC(O)N(R^4)_2$, $-N(R^9)_2$, $-C(O)C(O)OR^9$, $-(CH_2)_pN(R^9)_2$, $-N(R^4)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-(CH_2)_pS(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-NR^4S(O)_2R^9$, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_2-C_8alkene, C_1-C_8alkoxy, hydroxyl-substituted C_1-C_8alkyl, halo-substituted C_1-C_8alkyl and halo-substituted C_1-C_8alkoxy;

or R^6 is C_6-C_{14}aryl, C_2-C_{13}heteroaryl, C_2-C_{14}heterocycloalkyl or C_3-C_8cycloalkyl having a C_1-C_4alkyl bridge;

or R^6 is a C_2-C_{14}heterocycloalkyl optionally substituted with 1 to 3 substituents independently selected from halogen, =O, $-CN$, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^8$, $OC(O)N(R^4)_2$, $-N(R^9)_2$, $-C(O)C(O)OR^9$, $-(CH_2)_pN(R^9)_2$, $-N(R^4)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-(CH_2)_pS(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-NR^4S(O)_2R^9$, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_2-C_8alkene, C_1-C_8alkoxy, hydroxyl-substituted C_1-C_8alkyl, halo-substituted C_1-C_8alkyl and halo-substituted C_1-C_8alkoxy;

each R^7 is independently selected from H, C_1-C_8alkyl and $-L^1R^8$;

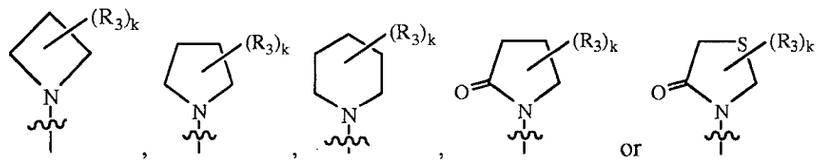
R^8 is H, $-N(R^9)_2$, $-N(R^4)_2$, $-SR^9$, $-CN$, C_1-C_8alkyl, C_3-C_8cycloalkyl and C_2-C_{14}heterocycloalkyl, wherein the C_1-C_8alkyl, C_3-C_8cycloalkyl and C_2-C_{14}heterocycloalkyl of R^8 are optionally substituted with 1 to 3 substituents independently selected from halogen, C_1-C_6alkyl, $-CN$, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-N(R^9)_2$, $-N(R^4)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, and $-NR^4S(O)_2$;

each R^9 is independently selected from H, C_3-C_8cycloalkyl and C_1-C_8alkyl,

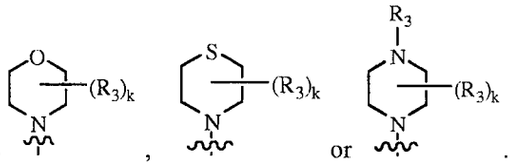
and

each p is independently 1, 2, 3, 4, 5 or 6.

2. The compound of claim 1, wherein

R^1 is  .

3. The compound of claim 1, wherein

R^1 is  .

4. The compound of any of claims 1-3, wherein each R^3 is independently selected from halogen, $-OR^9$, C_1-C_8alkyl, C_6-C_{14}aryl, C_3-C_8cycloalkyl, halo-substituted-C_1-C_8alkyl, C_2-C_{14}heterocycloalkyl and C_2-C_{13}heteroaryl, wherein the C_1-C_8alkyl, C_6-C_{14}aryl, C_3-C_8cycloalkyl, C_2-C_{14}heterocycloalkyl and C_2-C_{13}heteroaryl of R^3 are optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxyl, $-OR^9$, C_1-C_8alkyl, C_1-C_8alkoxy, hydroxyl-C_1-C_8alkyl, halo-substituted-C_1-C_8alkyl, halo-substituted-C_1-C_8alkoxy and C_3-C_8cycloalkyl.

5. The compound of any of claims 1-4, wherein the C_6-C_{14}aryl of R^3 is phenyl optionally substituted with 1 to 3 substituents independently selected from halogen, C_1-C_8alkyl, and halo-substituted-C_1-C_8alkyl.

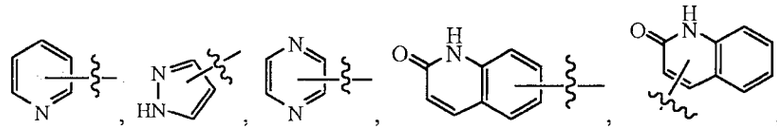
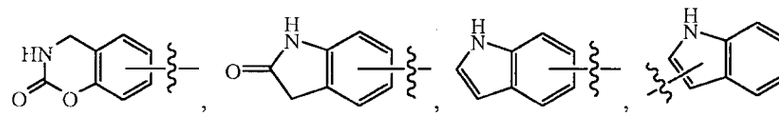
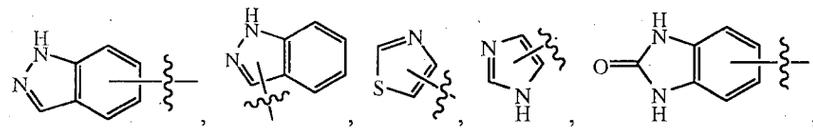
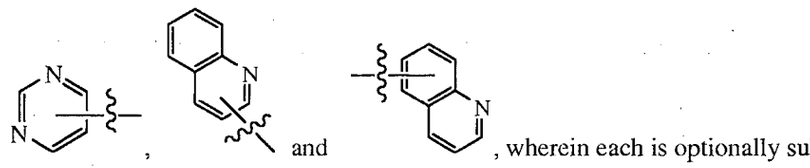
6. The compound of any of claims 1-5, wherein the C_6-C_{14}aryl of R^3 is phenyl optionally substituted with 1 to 3 substituents independently selected from fluoro and C_1-C_8alkyl.

7. The compound of any of claims 1-6, wherein R^2 is C_6-C_{14}aryl or C_2-C_{13}heteroaryl, wherein the C_6-C_{14}aryl and C_2-C_{13}heteroaryl of R^2 are optionally substituted with 1 to 3 substituents independently selected from halogen, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-OC(O)R^9$, C_1-C_8alkoxy, hydroxyl-C_1-C_8alkyl, halo-substituted C_1-C_8alkyl and halo-substituted C_1-C_8alkoxy.

8. The compound of any of claims 1-7, wherein R^2 is C_6-C_{14}aryl or C_2-C_{13}heteroaryl, wherein the C_6-C_{14}aryl and C_2-C_{13}heteroaryl of R^2 are optionally substituted with 1 to 3 substituents independently selected from halogen, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ and $-S(O)_2R^9$.

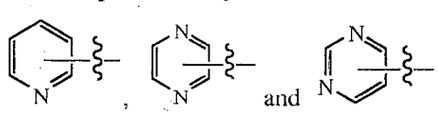
9. The compound of any of claims 1-8, wherein the C_6-C_{14}aryl of R^2 is phenyl optionally substituted with 1 to 3 substituents independently selected from halogen, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ and $-S(O)_2R^9$.

10. The compound of any of claims 1-8, wherein the C_2-C_{13}heteroaryl of R^2 is selected from

and , wherein each is optionally substituted with 1 to 3 substituents independently selected from halogen, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ and $-S(O)_2R^9$.

11. The compound of any of claims 1-8, wherein the C_2-C_{13}heteroaryl of R^2 is selected from

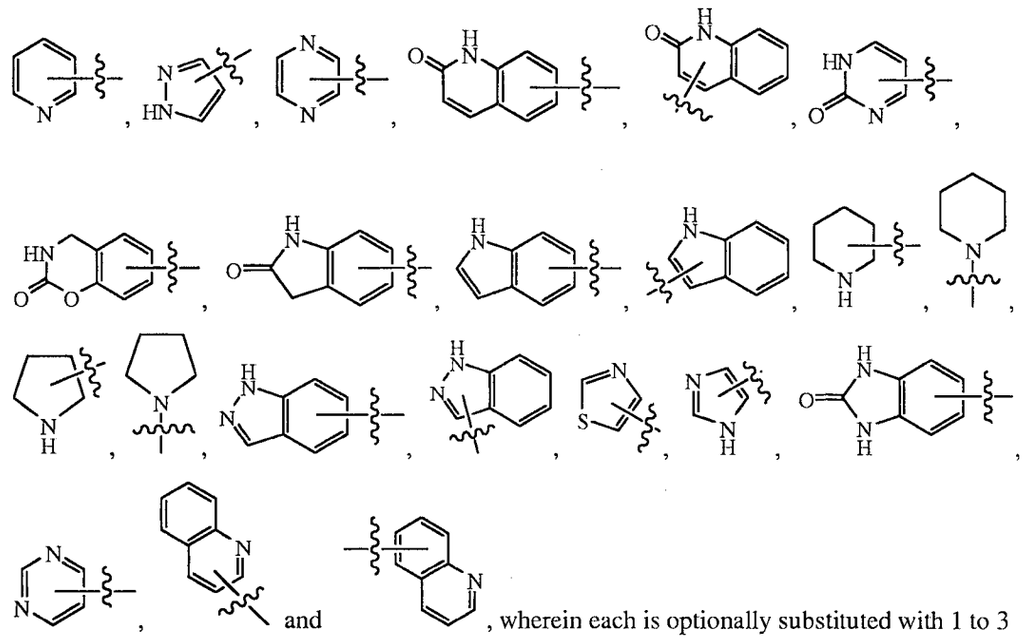


and , wherein each is optionally substituted with 1 to 3 substituents independently selected from halogen, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_3-C_8cycloalkyl, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ and $-S(O)_2R^9$.

12. The compound of any of claims 1-11, wherein R^6 is C_2-C_{13}heteroaryl, C_2-C_{14}heterocycloalkyl, $-OCH(R^7)_2$, C_1-C_8alkyl, or C_3-C_8cycloalkyl, wherein the C_1-C_8alkyl, C_3-C_8cycloalkyl, C_2-C_{13}heteroaryl, and C_2-C_{14}heterocycloalkyl of R^6 are optionally substituted with 1 to 3 substituents independently selected from halogen, $-CN$, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, -

L^1R^8, $-L^1R^5$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-N(R^4)_2$, $-S(O)_2R^9$, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_2-C_8alkene, and hydroxyl-substituted C_1-C_8alkyl.

13. The compound of any of claims 1-12, wherein R^6 is selected from

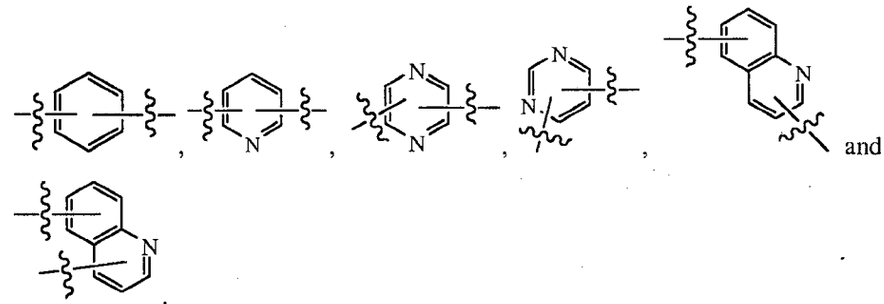


and

, wherein each is optionally substituted with 1 to 3 substituents independently selected from halogen, $-CN$, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-N(R^4)_2$, $-S(O)_2R^9$, C_2-C_{14}heterocycloalkyl, C_2-C_{13}heteroaryl, C_1-C_8alkyl, C_2-C_8alkene, and hydroxyl-substituted C_1-C_8alkyl.

14. The compound of any of claims 1-13, wherein Y^1 is C_6-C_{14}arylene or C_2-C_{13}heteroarylene.

15. The compound of any of claims 1-14, wherein Y^1 is selected from



and

16. The compound of any of claims 1-15, wherein each R^4 is independently selected from H, C_1-C_8 alkyl, C_6-C_{14}aryl , C_2-C_{14}heterocycloalkyl, $-L^1R^5$, $-L^1R^6$, $-L^1R^8$ and C_3-C_8cycloalkyl, wherein the

C_1-C_8alkyl, C_6-C_{14}aryl , C_2-C_{14}heterocycloalkyl, and C_3-C_8cycloalkyl are optionally substituted with $-(CH_2)_pOR^9$.

17. The compound of any of claims 1-16, wherein R^5 is C_6-C_{14}aryl, C_2-C_{13}heteroaryl, C_2-C_{14}heterocycloalkyl, $-N(R^9)_2$, $-N(R^9)C(O)R^9$, $-(CH_2)_pOR^9$, or $-OR^9$.

18. The compound of any of claims 1-17, wherein R^7 is $-L^1R^8$.

19. The compound of any of claims 1-18, wherein R^8 is $-N(R^9)_2$ or –CN.

20. The compound of claim 1 selected from:
(R)-1-(4-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)pyrrolidin-3-ol;
(R)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)piperidin-4-ol;
6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)indolin-2-one;
3-(6-((3S)-2-(3-fluorophenyl)-3-hydroxypyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
5-(6-(2-(2,5-dimethylphenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-fluorobenzonitrile;
(R)-4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
4-(5-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)morpholine;
4-(5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)morpholine;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-N-methylpicolinamide;
4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
5-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-N-methylpicolinamide;
(S)-4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
(R)-4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
4-(5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)morpholine;
4-(6-(2-phenylazetidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
(R)-4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
(S)-4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
4-(6-(2-(3-fluorophenyl)-2-methylpyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one;

6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)indolin-2-one;
6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)indolin-2-one;
4-(6-(2-(2,5-difluorophenyl)-5-methylpyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
4-(2-(4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1H-pyrazol-1-yl)ethyl)morpholine;
N-(2-(4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1H-pyrazol-1-yl)ethyl)acetamide;
(Z)-3-((1H-pyrrol-2-yl)methylene)-6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)indolin-2-one;
5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-fluorobenzonitrile;
5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-morpholinobenzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-fluorobenzonitrile;
5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(dimethylamino)benzonitrile;
5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-methylpiperazin-1-yl)benzonitrile;
5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-(2-methoxyethyl)piperazin-1-yl)benzonitrile;
5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-morpholinoethylamino)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(dimethylamino)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-methylpiperazin-1-yl)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-(2-methoxyethyl)piperazin-1-yl)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-morpholinoethylamino)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-morpholinobenzonitrile;
3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;

4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-morpholinopiperidin-1-yl)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(pyrrolidin-1-yl)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(3-(dimethylamino)pyrrolidin-1-yl)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2,6-dimethylmorpholino)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-(pyrrolidin-1-yl)ethoxy)benzonitrile;
5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)nicotinonitrile;
6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinonitrile;
4-(4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)thiazol-2-yl)morpholine;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(3-morpholinopropylamino)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(3-morpholinopyrrolidin-1-yl)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(1-methylpyrrolidin-3-yloxy)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-((2-(dimethylamino)ethyl)(methyl)amino)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-((1-methylpyrrolidin-3-yl)methoxy)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(3-morpholinopropoxy)benzonitrile;
3-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile;
4-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile;
3-(5-(2-(2,5-difluorophenyl)thiazolidin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile;
3-(5-(2-(2,5-difluorophenyl)thiazolidin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile;
3-(3-(1H-imidazol-2-yl)phenyl)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3H-imidazo[4,5-b]pyridine;
3-(5-(2-(2,5-difluorophenyl)-4-oxothiazolidin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile;
3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile;
4-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzonitrile;

3-(6-(2-(3-fluorophenyl)-3-oxopyrazolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
5-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)-2-(4-hydroxypiperidin-1-yl)benzonitrile;
2-(1,3-bis(dimethylamino)propan-2-yloxy)-4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(1-(dimethylamino)propan-2-yloxy)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-(1-methylpyrrolidin-2-yl)ethoxy)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(3-(dimethylamino)-2-hydroxypropoxy)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-((1-methylpyrrolidin-2-yl)methoxy)benzonitrile;
4-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
3-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
2-(2-(diethylamino)ethylamino)-4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
7-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-oxo-1,2-dihydroquinoline-3-carbonitrile;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-morpholinobenzonitrile;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-methylpiperazin-1-yl)benzonitrile;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-(2-methoxyethyl)piperazin-1-yl)benzonitrile;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-morpholinoethylamino)benzonitrile;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-morpholinopiperidin-1-yl)benzonitrile;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-(pyrrolidin-1-yl)ethoxy)benzonitrile;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-(1-methylpyrrolidin-2-yl)ethoxy)benzonitrile;
4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-methylpiperazin-1-yl)benzonitrile,

4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-(pyrrolidin-1-yl)ethoxy)benzonitrile;
4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-morpholinoethoxy)benzonitrile;
(R)-3-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
(S)-3-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
4-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
(R)-4-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
(S)-4-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
6-(6-(2-(2,5-dimethylphenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinic acid;
3-(6-((2R,4S)-3,3-difluoro-4-methyl-2-phenylpyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
3-(6-(2-phenylpyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
6-(6-(2-phenylpyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-((R)-pyrrolidin-2-ylmethoxy)benzonitrile;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-((S)-pyrrolidin-2-ylmethoxy)benzonitrile
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-(2-morpholino-2-oxoethyl)piperazin-1-yl)benzonitrile;
2-(4-(2-cyano-4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)phenyl)piperazin-1-yl)-N,N-dimethylacetamide;
2-(4-(3-(dimethylamino)propyl)piperazin-1-yl)-5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-hydroxypiperidin-1-yl)benzonitrile;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-(4-isopropylpiperazin-1-yl)ethoxy)benzonitrile;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(2-(4-(2-hydroxyethyl)piperazin-1-yl)ethoxy)benzonitrile;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(((R)-5-oxopyrrolidin-2-yl)methoxy)benzonitrile;
3-(6-((2R,4S)-3,3-difluoro-2-(3-fluorophenyl)-4-methylpyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;

6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(1H-indol-4-yl)imidazo[1,2-b]pyridazine;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(1-methyl-1H-indol-2-yl)imidazo[1,2-b]pyridazine;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(1H-indol-5-yl)imidazo[1,2-b]pyridazine;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(5-(4-methylpiperazin-1-yl)pyrazin-2-yl)imidazo[1,2-b]pyridazine;
4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(piperidin-1-yl)thiazole;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(5-(pyrrolidin-1-yl)pyrazin-2-yl)imidazo[1,2-b]pyridazine;
tert-butyl 4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazine-1-carboxylate;
3-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
tert-butyl 5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-methylphenylcarbamate;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(pyridin-2-yl)imidazo[1,2-b]pyridazine;
3-(6-chloropyrazin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine;
3-(6-(1H-imidazol-1-yl)pyrazin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine;
2-chloro-5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)thiazole;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-N,N-dimethylpyrazin-2-amine;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(piperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine;
4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)morpholine;
(S)-6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinonitrile;
(R)-6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinonitrile;
3-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)indolin-2-one;
6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(1H-indol-4-yl)imidazo[1,2-b]pyridazine;
4-(6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)morpholine;
6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(1H-indol-5-yl)imidazo[1,2-b]pyridazine;
(R)-4-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
(S)-4-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(1H-indazol-5-yl)imidazo[1,2-b]pyridazine;
3-(5-fluoro-6-methylpyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine;
3-(3-fluorophenyl)-4-(3-(pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;

6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)nicotinonitrile;
2-fluoro-5-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-methoxypyridin-2-yl)imidazo[1,2-b]pyridazine;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-fluoropyridin-2-yl)imidazo[1,2-b]pyridazine;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-N-(2-hydroxyethyl)picolinamide;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinamide;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(1H-indazol-6-yl)imidazo[1,2-b]pyridazine;
6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(1H-indazol-6-yl)imidazo[1,2-b]pyridazine;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(piperazin-1-yl)pyridin-3-yl)imidazo[1,2-b]pyridazine;
2-(4-(2-cyano-4-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)phenyl)piperazin-1-yl)-N,N-dimethylacetamide;
2-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-ylamino)ethanol;
1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol;
6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(6-fluoropyridin-2-yl)imidazo[1,2-b]pyridazine;
4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-2-one;
7-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-oxo-1,2-dihydroquinoline-3-carbonitrile;
4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(piperazin-1-ylmethyl)benzonitrile;
N1,N1-diethyl-N2-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)ethane-1,2-diamine;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(4-methylpiperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine;
(2S)-3-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-ylamino)propane-1,2-diol;
6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(6-(piperazin-1-yl)pyridin-3-yl)imidazo[1,2-b]pyridazine;
6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(6-(piperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine;
6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-(6-(4-methylpiperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine;

4-(6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-2-one;
(3S)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrrolidin-3-ol;
(3R)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrrolidin-3-ol;
(3S,4S)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrrolidine-3,4-diol;
3-(3-fluorophenyl)-4-(3-(5-(morpholinomethyl)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;
4-((6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-3-yl)methyl)morpholine;
4-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)-2-((4-methylpiperazin-1-yl)methyl)benzonitrile;
1-(6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol;
3-(3-fluorophenyl)-4-(3-(6-fluoropyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;
(5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)(4-hydroxypiperidin-1-yl)methanone;
3-(3-fluorophenyl)-4-(3-(6-morpholinopyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;
3-(3-fluorophenyl)-4-(3-(6-(piperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;
4-(6-(2-(2-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
3-(6-(2-(2-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
4-(4-(6-(2-(2-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)thiazol-2-yl)morpholine;
5-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)-2-(4-methylpiperazin-1-yl)benzonitrile;
2-(4-acetylpiperazin-1-yl)-5-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)benzonitrile;
5-(6-(2-(2-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(4-hydroxypiperidin-1-yl)benzonitrile;
1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol;
N-(5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyrazin-2-yl)cyclopropanecarboxamide;
4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-((4-methylpiperazin-1-yl)methyl)benzonitrile;

(2S)-4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-2-methylmorpholine;
1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carboxylic acid;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-methoxythiazole;
4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)thiazole-2-carboxylic acid;
(4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)thiazol-2-yl)methanol;
1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-3-ol;
(3R)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N,N-dimethylpyrrolidin-3-amine;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(1-methyl-1H-imidazol-2-yl)imidazo[1,2-b]pyridazine;
5-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)-2-(piperazin-1-yl)benzonitrile;
tert-butyl 4-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazine-1-carboxylate;
3-(3-fluorophenyl)-4-(3-(6-(4-methylpiperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;
4-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-2,6-dimethylmorpholine;
3-(3-fluorophenyl)-4-(3-(6-(piperidin-4-yloxy)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;
4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-(piperazin-1-ylmethyl)thiazole;
2,2'-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-ylazanediyl)diethanol;
4-(2-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yloxy)ethyl)morpholine;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)imidazo[1,2-b]pyridazine;
4-((6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)methyl)morpholine;
4-((6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)methyl)-2,6-dimethylmorpholine;
1-((6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)methyl)pyrrolidin-3-ol;

4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2-methoxythiazole;
ethyl 4-(5-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-1-carboxylate;
6-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)nicotinonitrile;
5-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)-1-(piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one;
2-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)-N,N-dimethylacetamide;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(4-isopropylpiperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine;
2-(1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-yl)propan-2-ol;
4-(1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-yl)morpholine;
3-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)propanenitrile;
1-(6-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol;
2-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)-N-isopropylacetamide;
(1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-yl)methanol;
(1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-3-yl)methanol;
1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carbonitrile;
2-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)ethanol;
(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)methanol;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(5-methyl-1H-imidazol-2-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine;
6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinamide;
(R)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-fluoropyridin-2-yl)imidazo[1,2-b]pyridazine;
(R)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol;

(1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-yl)methanol;

2-(1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-yl)ethanol;

1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-3-carboxamide;

1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carboxamide;

6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-ol;

6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinic acid;

2-fluoro-3-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)quinoline;

3-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)quinolin-2(1H)-one;

5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)quinoline;

6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(4-(methylsulfonyl)phenyl)imidazo[1,2-b]pyridazine;

6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(piperidin-4-yloxy)pyridin-2-yl)imidazo[1,2-b]pyridazine;

(1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-ylamino)cyclopentyl)methanol;

3-(3-fluorophenyl)-4-(3-(6-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;

3-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)quinoline;

(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)(4-hydroxypiperidin-1-yl)methanone;

6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(2-fluoropyridin-4-yl)imidazo[1,2-b]pyridazine;

1-(4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol;

N1,N1-diethyl-N2-(6-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)ethane-1,2-diamine;

6-(2-(3-fluorophenyl)piperidin-1-yl)-3-(6-(4-isopropylpiperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine;

(3S)-1-(6-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N,N-dimethylpyrrolidin-3-amine;

4-(3-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)-3-(3-fluorophenyl)morpholine;

6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)-N-(2-(piperazin-1-yl)ethyl)pyridin-2-amine;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(1-(methylsulfonyl)piperidin-4-yloxy)pyridin-2-yl)imidazo[1,2-b]pyridazine;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-a]pyridin-3-yl)-2-fluorobenzonitrile;
2-ethoxy-4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-a]pyridin-3-yl)thiazole;
5-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-a]pyridin-3-yl)-2-fluorobenzonitrile;
4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinic acid;
5-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)picolinic acid;
(2S,6R)-4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-2,6-dimethylmorpholine;
4-(6-(6-(2-(pyridin-2-yl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)morpholine;
1-(6-(6-(2-(pyridin-2-yl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol;
1-(6-(6-(2-(pyridin-3-yl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol;
6-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-N-methylpyridin-2-amine;
6-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-N-isopropylpyridin-2-amine;
N-(6-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)methanesulfonamide;
6-(6-(2-(3-fluorophenyl)piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-N,N-dimethylpyridin-2-amine;
6-(2-(3-fluorophenyl)piperidin-1-yl)-3-(6-(piperidin-4-yloxy)pyridin-2-yl)imidazo[1,2-b]pyridazine,
1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)azetidine-3-carboxylic acid;
1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)azetidin-3-ol;
4-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-a]pyridin-3-yl)-2-ethoxythiazole;
1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol;
(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)methanol;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(5-methyl-1H-imidazol-2-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine;
(1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-yl)methanol;

2-(4-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)ethanol;

1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-3-carboxamide;

1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carboxamide;

3-(3-fluorophenyl)-4-(3-(6-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;

4-(3-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)-3-(3-fluorophenyl)morpholine;

6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)-N-(2-(piperazin-1-yl)ethyl)pyridin-2-amine;

1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N-methylpiperidine-4-carboxamide;

1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N-(2-hydroxyethyl)piperidine-4-carboxamide;

(S)-6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)indolin-2-one;

(R)-6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)indolin-2-one;

(S)-1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol;

(R)-1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-ol;

ethyl 1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carboxylate;

3-(6-(1,3-dioxolan-2-yl)pyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine;

1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carboxylic acid;

5-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)oxazole;

3-(3-fluorophenyl)-4-(3-(6-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;

N-(cyclopropylmethoxy)-1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carboxamide;

1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N-isopropylpiperidine-4-carboxamide;

N-cyclopropyl-1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carboxamide;
1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N-(isoxazol-3-yl)piperidine-4-carboxamide;
(1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;
N-(cyanomethyl)-1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidine-4-carboxamide;
2-(1-(6-(6-(3-(3-fluorophenyl)morpholino)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperidin-4-yl)ethanol;
3-(6-(1H-pyrazol-5-yl)pyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine;
5-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carbonitrile;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(2-methylpyrimidin-4-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine;
4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-amine;
3-(6-((2R,5S)-2,5-dimethylpiperazin-1-yl)pyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine;
3-(6-((3S,5R)-3,5-dimethylpiperazin-1-yl)pyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine;
6-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2(1H)-one;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(4-(pyrazin-2-yl)piperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine;
4-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)morpholine;
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine;

2-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-ylamino)ethanol;

6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(6-(piperidin-4-yl)pyrimidin-4-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine;

2-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)-N,N-dimethylethanamine;

6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(pyrimidin-4-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine;

4-(1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrrolidin-3-yl)morpholine;

3-(6-(4-(cyclopropylsulfonyl)piperazin-1-yl)pyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine;

1-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)-2-hydroxyethanone;

(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)(1-hydroxycyclopropyl)methanone;

(R)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(2-methylpyrimidin-4-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine;

(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;

(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)piperazin-1-yl)(tetrahydrofuran-2-yl)methanone;

4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,3'-bipyridin-6'-yl)morpholine;

6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(5-(pyrrolidin-1-yl)pyrazin-2-yl)pyridin-2-yl)imidazo[1,2-b]pyridazine;

4-(5-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)morpholine;

1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)piperidin-4-ol;

N1-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)-N2,N2-dimethylethane-1,2-diamine;

1-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)piperidin-4-ol;

4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N,N-dimethylpyrimidin-2-amine;

3-(6-(1H-indazol-5-yl)pyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine;

2-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,3'-bipyridin-6'-ylamino)ethanol;

1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,3'-bipyridin-6'-yl)piperidin-4-ol;

(R)-2-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-ylamino)ethanol;

4-((S)-1-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrrolidin-3-yl)morpholine;

(2S,6R)-4-((S)-1-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrrolidin-3-yl)-2,6-dimethylmorpholine;

(R)-1-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)azetidin-3-ol;

(R)-N-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)methanesulfonamide;

(R)-4-((S)-1-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrrolidin-3-yl)-2-methylmorpholine;

(R)-2-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-ylamino)ethanol;

(R)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)azetidin-3-ol;

(R)-1-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)pyrrolidin-3-ol;

(R)-N-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)methanesulfonamide;

(R)-4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N-(pyridin-3-ylmethyl)pyrimidin-2-amine;

(S)-1-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)-N-methylpyrrolidin-3-amine;

(R)-4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N-(2-(methylsulfonyl)ethyl)pyrimidin-2-amine;

(R)-N-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,3'-bipyridin-6'-yl)methanesulfonamide;

(R)-3-(6-(1H-indazol-6-yl)pyridin-2-yl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine;

(R)-1-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)-N-methylpyrrolidin-3-amine;

(R)-1-(6'-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,2'-bipyridin-6-yl)piperidin-4-ol;

(R)-2-(6'-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,2'-bipyridin-6-ylamino)ethanol;

(R)-1-(6'-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,2'-bipyridin-6-yl)-N-methylpyrrolidin-3-amine;

(R)-1-(4-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)-N-methylpyrrolidin-3-amine;

(R)-2-(4-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)pyrimidin-2-yl)piperazin-1-yl)ethanol;

(R)-2-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)piperazin-1-yl)ethanol;

1-((2S,6R)-4-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-2,6-dimethylpiperazin-1-yl)-2-hydroxyethanone;

(R)-1-(6'-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,2'-bipyridin-6-yl)pyrrolidin-3-ol;

(R)-2-(4-(6'-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,2'-bipyridin-6-yl)piperazin-1-yl)ethanol;

(R)-4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)benzenesulfonamide;

(R)-3-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)benzenesulfonamide;

(R)-N-(6'-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,2'-bipyridin-6-yl)methanesulfonamide;

(R)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(2'-(piperazin-1-yl)-2,4'-bipyridin-6-yl)imidazo[1,2-b]pyridazine;

(R)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(6-(4-(methylsulfonyl)phenyl)pyridin-2-yl)imidazo[1,2-b]pyridazine;

(R)-4-(2-(4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-1H-pyrazol-1-yl)ethyl)morpholine;

(R)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-3-(2'-(4-isopropylpiperazin-1-yl)-2,4'-bipyridin-6-yl)imidazo[1,2-b]pyridazine;

(R)-4-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)pyridin-2-yl)-N-methylbenzenesulfonamide;

(S)-1-(6-(6-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)pyrrolidin-3-ol;

2-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-(piperidin-4-yloxy)pyridine;

{1-[(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)amino]cyclopentyl}methanol;

(3S,4S)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidine-3,4-diol;

1-{6-[6-(3-phenylthiomorpholin-4-yl)imidazo[1,2-b]pyridazin-3-yl]pyridin-2-yl}piperidin-4-ol;

2-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-[(1-methanesulfonylpiperidin-4-yl)oxy]pyridine;

(3S,4S)-1-(6-{6-[(2S)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidine-3,4-diol;

(3S,4S)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidine-3,4-diol;

4-(4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-1H-pyrazol-1-yl)piperidine;

N-[(3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-N-methylmethanesulfonamide;

2-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-(3-fluoropiperidin-1-yl)pyridine;

N-[(3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-N-methylacetamide;

N-[(3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-2-hydroxy-N-methylacetamide;

2-(3,3-difluoropiperidin-1-yl)-6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine;

N-ethyl-N-[(3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]acetamide;

N-ethyl-N-[(3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-2-hydroxyacetamide;

N-[(3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]methanesulfonamide;

N-[1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl]-N-methylmethanesulfonamide;

N-[1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl]acetamide;

1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-3-methylpiperidin-4-ol;

1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-amine;

2,2,2-trifluoro-N-[(3S)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]acetamide;

N-[(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]methanesulfonamide;

N-ethyl-N-[(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]acetamide;

N-[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-yl]-N-methylmethanesulfonamide;

(3S)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-amine;

2-(dimethylamino)-1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]ethan-1-one;

(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-3-methylpiperazine;

2-[(2R)-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-2-methylpiperazin-1-yl]-2-oxoethyl acetate;

1-[(2R)-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-2-methylpiperazin-1-yl]-2-hydroxyethan-1-one;

2-amino-1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]ethan-1-one;

1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-2-(methylamino)ethan-1-one;

2-(dimethylamino)-1-[(2R)-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-2-methylpiperazin-1-yl]ethan-1-one;
(3R)-3-{[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]carbonyl}morpholine;
(3R)-3-{[(2R)-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-2-methylpiperazin-1-yl]carbonyl}morpholine;
8-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-octahydropiperazino[2,1-c]morpholin-4-one;
(3R,4R)-1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyridin-2-yl]pyrrolidine-3,4-diol;
1-(6-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-ol;
6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine-2-carboxamide;
6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-ol;
6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine-2-carboxylic acid;
2-fluoro-3-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}quinoline;
3-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-1,2-dihydroquinolin-2-one;
5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}quinoline;
2-(3-fluorophenyl)-1-[3-(4-methanesulfonylphenyl)imidazo[1,2-b]pyridazin-6-yl]pyrrolidine;
3-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}quinoline;
1-[(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)carbonyl]piperidin-4-ol;
2-fluoro-4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine;
1-(4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-ol;
1-(4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-methylpiperazine;
2-[(4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)amino]ethan-1-ol;
(3R)-1-[(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)carbonyl]-N,N-dimethylpyrrolidin-3-amine;
1-(5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrimidin-2-yl)piperidin-4-ol;

6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-N-methylpyridine-2-carboxamide;

4-[(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)carbonyl]morpholine;

(3R)-1-(4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-ol;

(3S)-1-(4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-ol;

(3R,4R)-1-(4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidine-3,4-diol;

1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N,N-dimethylpiperidin-4-amine;

2-[(5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrimidin-2-yl)amino]ethan-1-ol;

5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-N-methylpyrimidin-2-amine;

5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-N,N-dimethylpyrimidin-2-amine;

1-(4-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N,N-dimethylpiperidin-4-amine;

2-chloro-5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrimidine;

tert-butyl 4-[(5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrimidin-2-yl)oxy]piperidine-1-carboxylate;

5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-2-(piperidin-4-yloxy)pyrimidine;

1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N,N-dimethylpiperidin-4-amine;

5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrimidine;

5-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-1,2-dihydropyrimidine;

1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-one;

1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazine;

6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-N-[1-(propan-2-yl)piperidin-4-yl]pyridin-2-amine;

[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl] carbamate;
1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl N-methylcarbamate;
1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl N-tert-butylcarbamate;
1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]ethan-1-one;
N,N-diethyl-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-amine;
2,2,2-trifluoro-1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]ethan-1-one;
1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-methanesulfonylpiperazine;
2-(benzyloxy)-1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]ethan-1-one;
1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-2-hydroxyethan-1-one;
2-{[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl]amino}ethan-1-ol;
2-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-(1,2,3,6-tetrahydropyridin-1-yl)pyridine;
N,N-diethyl-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-amine;
N-cyclopropyl-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-amine;
(3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-methylpyrrolidin-3-amine;
(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-methylpyrrolidin-3-amine;
1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-methylpiperidin-4-amine;
2-fluoro-N-[1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-N,2-dimethylpropanamide;

2-fluoro-N-[1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-N-methylpropanamide;

1-tert-butyl-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazine;

1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidine-3-carboxylic acid;

2-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-[4-(pyrrolidin-1-yl)piperidin-1-yl]pyridine;

2-fluoro-N-[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl]-N,2-dimethylpropanamide;

2,2,2-trifluoro-N-[(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-N-methylacetamide;

6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-N-methyl-N-(piperidin-4-yl)pyridin-2-amine;

2-fluoro-N-[(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-N,2-dimethylpropanamide;

[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-yl]methanol;

(3R)-N-(2-fluoro-2-methylpropyl)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-methylpyrrolidin-3-amine;

1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-(propane-2-sulfonyl)piperazine;

1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-[(2-methylpropane)sulfonyl]piperazine;

1-(butane-2-sulfonyl)-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazine;

1-(ethanesulfonyl)-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazine;

(3S)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-methylpyrrolidin-3-amine;

(3S)-N-ethyl-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-amine;

(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-(2,2,2-trifluoroethyl)pyrrolidin-3-amine;

2-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-2-oxoethyl acetate;

{[(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]carbamoyl}methyl acetate;

N-[(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-2-hydroxyacetamide;

4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-1-methylpiperazin-2-one;

4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-1-(2-hydroxyethyl)piperazin-2-one;

2-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-[4-(piperidin-1-yl)piperidin-1-yl]pyridine;

{[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl]methyl}dimethylamine;

2-(4,4-dimethylpiperidin-1-yl)-6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine;

2-(3,3-dimethylpiperidin-1-yl)-6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine;

4-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]benzoic acid;

1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-2-methyl-1-oxopropan-2-yl acetate;

(2S)-1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-1-oxopropan-2-yl acetate;

1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N,N-dimethylpiperidin-4-amine;

N,N-diethyl-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazine-1-sulfonamide;

N-ethyl-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-methylpiperidin-4-amine;

(2S)-1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-2-hydroxypropan-1-one;

1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-2-hydroxy-2-methylpropan-1-one;

8-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane;

4-ethyl-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-ol;

1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-(propan-2-yl)piperidin-4-ol;

4-ethenyl-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-ol;

1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-methylpiperidin-4-ol;

2-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-{octahydropyrrolo[1,2-b]piperazin-2-yl}pyridine;

8-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-3-methyl-1,3,8-triazaspiro[4.5]decane-2,4-dione;

(1S)-1-{[(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]carbamoyl}ethyl acetate;

(2S)-N-[(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]-2-hydroxypropanamide;

1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-3-(trifluoromethyl)piperazine;

1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-methylpiperidin-3-amine;

1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyridin-2-yl]-N,N-dimethylpiperidin-4-amine;

2-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-2-(trifluoromethyl)piperazin-1-yl]-2-oxoethyl acetate;

1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-2-(trifluoromethyl)piperazin-1-yl]-2-hydroxyethan-1-one;

1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyridin-2-yl]-N-methylpiperidin-4-amine;

4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyridin-2-ol;

N-cyclobutyl-6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-amine;

N-cyclopropyl-6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-amine;
N-cyclopropyl-1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyridin-2-yl]piperidin-4-amine;
1-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyridin-2-yl]piperidin-4-one;
1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-(pyridin-3-yl)piperazine;
1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-(pyridin-2-yl)piperazine;
1-(4-fluorophenyl)-4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazine;
1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-(6-methylpyridin-2-yl)piperazine;
1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine;
2-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-N-methyl-N-phenylacetamide;
2-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-2-oxoacetic acid;
6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine-2-carboxamide;
6-{6-[(2S)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine-2-carboxamide;
2-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]ethan-1-ol;
2-[4-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]-N-(propan-2-yl)acetamide;
[1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-yl]methanol;
[1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-3-yl]methanol;
1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidine-4-carbonitrile;

141

2-[4-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperazin-1-yl]ethan-1-ol;

1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-ol;

2-fluoro-6-{6-[(2S)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine;

2-fluoro-6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridine;

diethyl({2-[(6-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)amino]ethyl})amine;

1-(6-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-4-(propan-2-yl)piperazine;

(3S)-1-(6-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N,N-dimethylpyrrolidin-3-amine;

6-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-N-methylpyridin-2-amine;

6-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-N-(propan-2-yl)pyridin-2-amine;

N-(6-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)methanesulfonamide;

6-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-N,N-dimethylpyridin-2-amine;

2-{6-[2-(3-fluorophenyl)piperidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-(piperidin-4-yloxy)pyridine;

1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-ol;

(3R)-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N,N-dimethylpyrrolidin-3-amine;

1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-N-(2-hydroxyethyl)piperidine-4-carboxamide;

N-[2-(dimethylamino)ethyl]-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidine-4-carboxamide;

1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidine-3-carboxylic acid;

N-(cyanomethyl)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidine-4-carboxamide;

2-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrazine;

N-[(3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrrolidin-3-yl]acetamide;

1-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-1H-pyrazole;

1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrazin-2-yl)piperidin-4-ol;

(3S)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrazin-2-yl)-N,N-dimethylpyrrolidin-3-amine;

2-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-6-(piperazin-1-yl)pyrazine;

2-[4-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrazin-2-yl)piperazin-1-yl]ethan-1-ol;

(3R)-1-(6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyrazin-2-yl)-N,N-dimethylpyrrolidin-3-amine;

N-[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-yl]acetamide;

1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-amine;

N-[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-yl]methanesulfonamide;

N-ethyl-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-amine;

N,N-diethyl-1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-amine;

3-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-1H-pyrrole;

N-[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-yl]-2-hydroxyacetamide;

N-ethyl-N-[1-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)azetidin-3-yl]methanesulfonamide;

1-[6-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyridin-2-yl]piperidin-4-ol;

6-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)-2-oxa-6-azaspiro[3.3]heptane;

6-[4-(6-{6-[(2R)-2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)pyrimidin-2-yl]-2-oxa-6-azaspiro[3.3]heptane;

6-{6-[2-(3-fluorophenyl)pyrrolidin-1-yl]imidazo[1,2-b]pyridazin-3-yl}-2,3-dihydro-1H-indol-2-one;

6-{6-[3-(3-fluorophenyl)morpholin-4-yl]imidazo[1,2-b]pyridazin-3-yl}-2,3-dihydro-1H-indol-2-one;

3-(3-fluorophenyl)-4-{3-[6-(piperazin-1-yl)pyridin-2-yl]imidazo[1,2-b]pyridazin-6-yl}morpholine;

(3S)-4-[3-(6-fluoropyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl]-3-phenylmorpholine;

1-(6-{6-[(3S)-3-phenylmorpholin-4-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidin-4-ol;

1-(6-{6-[3-(3-fluorophenyl)morpholin-4-yl]imidazo[1,2-b]pyridazin-3-yl}pyridin-2-yl)piperidine-4-carbaldehyde;

3-(3-fluorophenyl)-4-(3-{6-[4-(4-methyl-1H-imidazol-2-yl)piperidin-1-yl]pyridin-2-yl}imidazo[1,2-b]pyridazin-6-yl)morpholine;

6-{6-[3-(3-fluorophenyl)morpholin-4-yl]imidazo[1,2-b]pyridazin-3-yl}-N,N-dimethylpyridin-2-amine;

3-(3-fluorophenyl)-4-[3-(6-{4-[2-(methylsulfanyl)ethyl]piperazin-1-yl}pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl]morpholine;

3-(3-fluorophenyl)-4-(3-{6-[4-(2-methanesulfonylethyl)piperazin-1-yl]pyridin-2-yl}imidazo[1,2-b]pyridazin-6-yl)morpholine;

(N-cyclopropyl-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-2,4'-bipyridin-2'-yl)piperidin-4-amine);

3-(3-fluorophenyl)-4-(3-{6-[4-(1H-1,2,4-triazol-5-yl)piperidin-1-yl]pyridin-2-yl}imidazo[1,2-b]pyridazin-6-yl)morpholine, and

3-(3-fluorophenyl)-4-(3-{6-[4-(1,2,4-oxadiazol-5-yl)piperidin-1-yl]pyridin-2-yl}imidazo[1,2-b]pyridazin-6-yl)morpholine.

21. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any of claims 1-20 and a pharmaceutically acceptable carrier.

22. The pharmaceutical composition of claim 21, wherein the pharmaceutical composition is formulated for intravenous, oral administration, rectal administration inhalation, nasal administration, topical administration, ophthalmic administration or otic administration.

23. The pharmaceutical composition of claim 21 or claim 22, wherein the pharmaceutical composition is 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.

24. A medicament for treating a kinase-mediated disease or condition in a patient comprising a therapeutically effective amount of a compound of any of claims 1-20, wherein the kinase is

selected from Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and ALK.

25. Use of a compound of any of claims 1-20 in the manufacture of a medicament for treating a kinase-mediated disease or condition, wherein the kinase is selected from Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and ALK.

26. A method for inhibiting a kinase, comprising administering to a system or a subject in need thereof, a therapeutically effective amount of a compound any of claims 1-20, or pharmaceutically acceptable salts or pharmaceutical compositions thereof, thereby inhibiting the kinase.

27. The method of claim 26, wherein the kinase is selected from Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and ALK or a combination thereof.

28. The method of claim 26, wherein the kinase is TrkA, TrkB, TrkC or ALK.

29. A method for treating a kinase-mediated disease or condition, comprising administering to a system or subject in need of such treatment an effective amount of a compound of any of claims 1-20, or pharmaceutically acceptable salts or pharmaceutical compositions thereof, thereby treating the condition, and wherein the kinase is selected from Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and ALK or a combination thereof.

30. The method of claim 29, wherein the disease or condition is cancer, a proliferative diseases, a pain disorder, a dermatological disease, a metabolic disease, a muscle disease, a neurodegenerative disease, a neurological disease, an immunodeficiency disease, an immunologically-mediated disease, an autoimmune disease, an autoimmune mediated disease, a bone disease, an inflammatory disease, fibrosis, an ophthalmic disease, an infectious disease, a viral disease, wound repair, a respiratory disease, a pulmonary disease, a renal disease, a kidney disease, a liver disease, a cardiovascular disease, a vascular disease, heart disease, cell death and hyperplasiaan inflammatory disease.

31. The method of claim 30, wherein the disease or condition is asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohns disease, bronchitis, dermatitis, allergic rhinitis, psoriasis, scleroderma, urticaria, rheumatoid arthritis, multiple sclerosis, lymphoma, metastasis, anaplastic large-cell lymphoma, osteosarcoma, fibrosarcoma, melanoma, breast cancer, renal cancer, brain cancer,

prostate cancer, colorectal cancer, thyroid cancer, ovarian cancer, pancreatic cancer, neuronal cancer, neuroblastoma, lung cancer, uterine cancer, gastrointestinal cancer, HIV or lupus.

32. 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 1-20, or pharmaceutically acceptable salts or pharmaceutical compositions thereof; wherein the cell-proliferative condition is lymphoma, metastasis, anaplastic large-cell lymphoma, osteosarcoma, fibrosarcoma, melanoma, breast cancer, renal cancer, brain cancer, prostate cancer, colorectal cancer, thyroid cancer, ovarian cancer, pancreatic cancer, neuronal cancer, neuroblastoma, lung cancer, uterine cancer or gastrointestinal cancer.

33. The method for claim 32, wherein the cell-proliferative condition is anaplastic large-cell lymphoma, pancreatic cancer, ovarian cancer and lung cancer.

34. A compound for use in a method of medical treatment, wherein the method of medical treatment is for treating a disease selected from cancer, a proliferative diseases, a pain disorder, a dermatological disease, a metabolic disease, a muscle disease, a neurodegenerative disease, a neurological disease, an immunodeficiency disease, an immunologically-mediated disease, an autoimmune disease, an autoimmune mediated disease, a bone disease, an inflammatory disease, fibrosis, an ophthalmic disease, an infectious disease, a viral disease, wound repair, a respiratory disease, a pulmonary disease, a renal disease, a kidney disease, a liver disease, a cardiovascular disease, a vascular disease, heart disease, cell death and hyperplasiaan inflammatory disease, and wherein the compound is a compound of any of claims 1-20.

35. The compound of claim 34, wherein the disease is asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohns disease, bronchitis, dermatitis, allergic rhinitis, psoriasis, scleroderma, urticaria, rheumatoid arthritis, multiple sclerosis, lymphoma, metastasis, anaplastic large-cell lymphoma, osteosarcoma, fibrosarcoma, melanoma, breast cancer, renal cancer, brain cancer, prostate cancer, colorectal cancer, thyroid cancer, ovarian cancer, pancreatic cancer, neuronal cancer, neuroblastoma, lung cancer, uterine cancer, gastrointestinal cancer, HIV or lupus.

SOLICITUD INTERNACIONAL PUBLICADA:DE ACUERDO CON EL TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES (TCP)

(19) Organización Mundial de la Propiedad Intelectual
Oficina Internacional

(43) Fecha de Publicación Internacional
19 de Noviembre de 2009 (19.11.2009)

(10) Número de Publicación Internacional
PCT **WO 2009/140128 A3**

(51) Clasificación Internacional de Patente:
C07D 471/04 (2006.01) ***A61K 31/4985*** (2006.01)
C07D 487/04 (2006.01) ***A61P 37/00*** (2006.01)
A61K 31/4353 (2006.01)

(21) Número de Solicitud Internacional:
PCT/US2009/043073

(22) Fecha de Presentación Internacional:
07 de Mayo de 2009 (07.05.2009)

(25) Idioma de Presentación: Inglés

(26) Idioma de Publicación: Inglés

(30) Información de Prioridad
61/052,879 13 de Mayo de 2008 (13.05.2008) US
61/152,872 16 de Febrero de 2009 (16.02.2009) US

(71) Solicitante *(para todos los Estados (Países) designados excepto US)*: **IRM LLC** [US/US]; 131 Front Street, P.O Box 2899, Bermuda, Hamilton HM LX (BM).

(72) Inventores; e

(75) Inventores/Solicitantes *(para US solamente)*: **ALBAUGH, Pamela, A.** [US/US]; 6081 Paseo Monona, Carlsbad, CA 92009 (US). **CHOI, Ha-Soon** [KR/US]; 13716 Fontanelle Place, San Diego, CA 92128 (US). **CHOPIUK, Gregory** [CA/US]; 10994 West Ocean Air Drive, Apt. 387, San Diego, CA 92130 (US). **FAN, Yi** [CN/US]; 12228 Pepper Tree Lane, Poway, CA 92064 (US). **RUCKER, Paul, Vincent** [US/US]; 2390 Rising Glen Way, Apt. 101, Carlsbad, CA 92008 (US). **WANG, Zhicheng** [CN/US]; 13012 Chambord Way, San Diego, CA 92130 (US).

(74) Agente : RAYMOND, Daniel, E. y colaboradores; Genomics Institute of the Novartis Research Foundation, 10675 John Jay Hopkins Drive, San Diego, CA 92121 (US).

(81) Estados (Países) Designados (*a menos que se indique de otra manera, para cada tipo de protección nacional disponible*): 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, 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) Estados (Países) Designados (*a menos que se indique de otra manera, para cada tipo de protección regional disponible*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasiáticos (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europeos (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).

Publicada:

-- *con reporte de búsqueda internacional (Art. 21(3))*

-- *antes del vencimiento del límite de tiempo para enmendar las reivindicaciones, y para volverse a publicar en el caso de recibirse las enmiendas (Regla 48.2(h))*

(88) Fecha de publicación del reporte de búsqueda internacional: 7 de Enero de 2010

(54) Título : HETEROCICLOS QUE CONTIENEN NITRÓGENO FUSIONADO Y COMPOSICIONES DE LOS MISMOS COMO INHIBIDORES DE CINASA

(57) Resumen:

La invención proporciona compuestos, composiciones farmacéuticas que comprenden estos compuestos, y métodos para utilizar tales compuestos con el fin de tratar o prevenir las enfermedades o los trastornos asociados con una actividad de cinasa anormal o mal regulada, en particular de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y ALK, o combinaciones de las mismas.

HETEROCICLOS QUE CONTIENEN NITRÓGENO FUSIONADO Y COMPOSICIONES DE LOS MISMOS COMO INHIBIDORES DE CINASA

REFERENCIA CRUZADA A SOLICITUDES RELACIONADAS

Esta solicitud reivindica el beneficio de prioridad de acuerdo con el Título 35 del Código de los Estados Unidos Sección 119(e), a la Solicitud Provisional de Patente de los Estados Unidos de Norteamérica Número 61/052,879, presentada el 13 de Mayo de 2008 y a la Solicitud Provisional de Patente de los Estados Unidos de Norteamérica Número 61/152,872, presentada el 16 de Febrero de 2009. La divulgación de las solicitudes de prioridad se incorpora a la presente como referencia en su totalidad y para todos los propósitos.

CAMPO DE LA INVENCIÓN

La invención se refiere a inhibidores de cinasa de proteína, y a métodos para utilizar estos compuestos.

ANTECEDENTES DE LA INVENCIÓN

Las cinasas de proteína (PK) son un gran conjunto de fosforil-transferasas estructuralmente relacionadas que tienen estructuras y funciones catalíticas altamente conservadas. Las cinasas de proteína son componentes enzimáticos de las sendas de transducción de señales que catalizan la transferencia del fosfato terminal desde el ATP hasta el grupo hidroxilo de los residuos de tirosina, serina y/o treonina de las proteínas, y, por consiguiente se categorizan en familias por los sustratos que fosforilan: Cinasas de Proteína

Tirosina (PTK), y Cinasas de Proteína de Serina/Treonina.

Las cinasas de proteína tienen una función crítica en el control del crecimiento y diferenciación celular, y son responsables del control de una amplia variedad de procesos de transducción de señales celulares, en donde las cinasas de proteína son mediadores clave de las señales celulares que conducen a la producción de los factores de crecimiento y las citoquinas. La sobre-expresión o la expresión inapropiada de las cinasas de proteína normales o mutantes tiene una función significativa en el desarrollo de muchas enfermedades y trastornos, incluyendo los trastornos del sistema nervioso central, tales como enfermedad de Alzheimer, trastornos inflamatorios, tales como artritis, enfermedades óseas tales como osteoporosis, trastornos metabólicos, tales como diabetes, trastornos proliferativos de los vasos sanguíneos, tales como angiogénesis, enfermedades autoinmunes tales como artritis reumatoide, enfermedades oculares, enfermedades cardiovasculares, ateroesclerosis, cáncer, trombosis, soriasis, restenosis, esquizofrenia, sensación de dolor, rechazo de trasplante, y enfermedades infecciosas, tales como infecciones virales y fúngicas.

Los ejemplos de las cinasas de proteína tirosina incluyen, pero no se limitan a, Irk, IGFR-1, Zap-70, Bmx, Btk, CHK (cinasa homóloga de Csk), CSK (cinasa Src C-terminal), Itk-1, Src (c-Src, Lyn, Fyn, Lck, Syk, Hck, Yes, Blk, Fgr, y Frk), Tec, Txk/Rlk, Abl, EGFR (EGFR-1/ErbB-1, ErbB-2/NEU/HER-2, ErbB-3, y ErbB-4), FAK, FGF1R (también FGFR1 o FGR-1), FGF2R (también FGR-2), MET

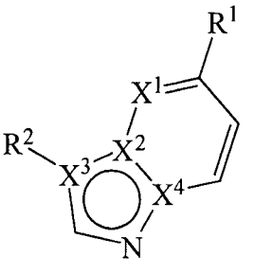
(también Met-I o c-MET), PDGFR (α y ß), Tie-1, Tie-2 (también Tek-1 o Tek), VEGFR1 (también FLT-1), VEGFR2 (también KDR), FLT-3, FLT-4, c-KIT, JAK1, JAK2, JAK3, TYK2, LOK, RET, TRKA, TRKB, TRKC, PYK2, ALK (Cinasa de Linfoma Anaplásico), EPHA (1-8), EPHB (1-6), RON, Ros, Fes, Fer, o EPHB4 (también EPHB4-1).

Los ejemplos de las cinasas de proteína serina/treonina incluyen, pero no se limitan a, Ark, ATM (1-3), CamK (1-IV), CamKK, Chk1 y 2 (cinasas Checkpoint), CKI, CK2, Erk, IKK-I (también IKK-ALFA o CHUK), IKK-2 (también IKK-BETA), Ilk, Jnk (1-3), LimK (1 y 2), MLK3Raf (A, B, y C), CDK (1-10), PKC (incluyendo todos los subtipos de PKC), Plk (1-3), NIK, Pak (1-3), PDK1, PKR, RhoK, RIP, RIP-2, GSK3 (α y ß), PKA, P38, Erk (1-3), PKB (incluyendo todos los subtipos de PKB) (también AKT-1, AKT-2, AKT-3, o AKT3-1), IRAK1, FRK, SGK, TAK1, o Tp1-2 (también COT).

BREVE DESCRIPCIÓN DE LA INVENCIÓN

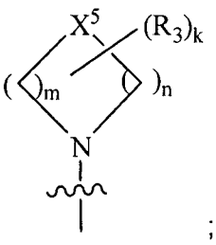
En la presente se proporcionan compuestos y composiciones farmacéuticas de los mismos, los cuales son útiles como inhibidores de cinasa de proteína.

En un aspecto, la presente invención proporciona compuestos que tienen la fórmula (I), y las sales farmacéuticamente aceptables, los solvatos farmacéuticamente aceptables (por ejemplo, hidratos), los derivados de N-óxido, derivados de pro-fármaco, derivados protegidos, los isómeros individuales y mezclas de isómeros de los mismos:



Fórmula (I)

en donde:

R^1 es  ; en donde:

X^1, X^2, X^3 y X^4 son cada uno independientemente CR^9 o N, con la condición de que cuando menos uno de X^1, X^2 X^3 y X^4 es N, y cuando mucho solamente dos de X^1, X^2, X^3 y X^4 son N;

X^5 es $C(R^3)_2$, O, S, $S(O)_2$, S(O), o NR^3;

m es 1, 2, 3 ó 4;

n es 0, 1, 2 ó 3;

k es 0, 1, 2, 3, 4, 5 ó 6;

cada R^3 se selecciona independientemente a partir de halógeno, nitro, $-N(R^4)_2$, $-OR^9$, -CN, =O, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-C(O)OR^9$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, $-OC(O)R^9$, $-(CH_2)_p$

OR^9, $-L^1C(O)R^8$, $-L^1R^8$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, alquilo de 1 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono y heteroarilo de 2 a 13 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono y heteroarilo de 2 a 13 átomos de carbono de R^3 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, amino, nitro, hidroxilo, ciano, $-OR^9$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-C(O)OR^9$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, $-OC(O)R^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, alquilo de 1 a 8 átomos de carbono, amino-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno, cicloalquilo de 3 a 8 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de

carbono, arilo de 6 a 14 átomos de carbono, y heteroarilo de 2 a 13 átomos de carbono;

de una manera alternativa, cada R^3 es independientemente un alquilo de 1 a 8 átomos de carbono, en donde cuando menos dos R^3 forman juntos un cicloalquilo de 3 a 8 átomos de carbono fusionado con un heterociclo, y en donde cada alquilo de 1 a 8 átomos de carbono de R^3 está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, amino, nitro, hidroxilo, ciano, $-OR^9$, alquilo de 1 a 8 átomos de carbono, amino-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno, cicloalquilo de 3 a 8 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, arilo de 6 a 14 átomos de carbono, y heteroarilo de 2 a 13 átomos de carbono;

R^2 es arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono o hetero-cicloalquilo de 2 a 14 átomos de carbono, en donde el arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono o hetero-cicloalquilo de 2 a 14 átomos de carbono de R^2 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$,

$-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-OC(O)R^9$, alcoxilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno y alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno;

cada R^4 se selecciona independientemente a partir de H, alquilo de 1 a 8 átomos de carbono, $-L^1R^5$, $-L^1R^6$, $-L^1R^8$, heteroarilo de 2 a 13 átomos de carbono, arilo de 6 a 14 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, y cicloalquilo de 3 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, y cicloalquilo de 3 a 8 átomos de carbono están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, deuterio, $-CD_3$, $-S(O)_2R^9$, -CN, alquilo de 1 a 8 átomos de carbono, $-OR^9$, $-N(R^9)_2$ y $-(CH_2)_pOR^9$;

L^1 es un enlace, alquileno de 1 a 8 átomos de carbono, alquenileno de 2 a 8 átomos de carbono, $-O(CH_2)_p-$, -C(O)-, $-N(R^9)-$, $(CH_2)_pC(O)-$, $-C(O)-(CH_2)_pO(CH_2)_p-$ o -C(O)O-;

Y^1 es arileno de 6 a 14 átomos de carbono, heteroarileno de 2 a 13 átomos de carbono, cicloalquileno de 3 a 8 átomos de carbono, hetero-cicloalquileno de 2 a 14 átomos de carbono, o alcoxileno de 1 a 8 átomos de carbono, cada uno de los cuales está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de

carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-OC(O)R^9$, alcoxilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, y alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno;

R^5 es arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, $-N(R^9)_2$, $-N(R^9)C(O)R^9$, $-C(O)N(R^9)_2$, $-(CH_2)_pOR^9$ u $-OR^9$.

R^6 es arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, $-OCH(R^7)_2$, $-OCH(R^7)_2$, $-C(O)R^7$, alquilo de 1 a 8 átomos de carbono, o cicloalquilo de 3 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, y hetero-cicloalquilo de 2 a 14 átomos de carbono de R^6 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, $-CN$, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^8$, $OC(O)N(R^4)_2$, $-N(R^9)_2$, $-C(O)C(O)OR^9$, $-(CH_2)_pN(R^9)_2$, $-N(R^4)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-(CH_2)_pS(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-NR^4S(O)_2R^9$, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13

átomos de carbono, alquilo de 1 a 8 átomos de carbono, alqueno de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por hidroxilo, alquilo de 1 a 8 átomos de carbono sustituido por halógeno y alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno;

o R^6 es arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono o cicloalquilo de 3 a 8 átomos de carbono que tiene un puente de alquilo de 1 a 4 átomos de carbono;

o R^6 es un hetero-cicloalquilo de 2 a 14 átomos de carbono opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados a partir de halógeno, =O, -CN, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^8$, $OC(O)N(R^4)_2$, $-N(R^9)_2$, $-C(O)C(O)OR^9$, $-(CH_2)_pN(R^9)_2$, $-N(R^4)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-(CH_2)_pS(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-NR^4S(O)_2R^9$, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, alqueno de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por hidroxilo, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, y alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno;

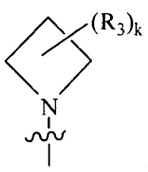
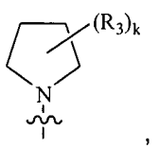
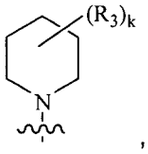
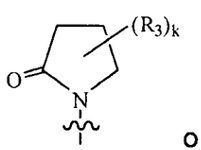
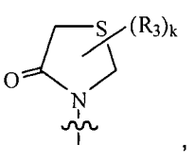
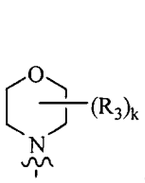
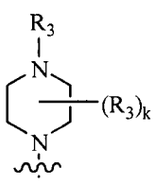
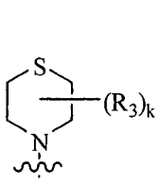
cada R^7 se selecciona independientemente a partir de H, alquilo de 1 a 8 átomos de carbono y $-L^1R^8$;

R^8 es H, $-N(R^9)_2$, $-N(R^4)_2$, $-SR^9$, -CN, alquilo de 1 a 8 átomos de

carbono, cicloalquilo de 3 a 8 átomos de carbono y hetero-cicloalquilo de 2 a 14 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono y hetero-cicloalquilo de 2 a 14 átomos de carbono de R^8 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, alquilo de 1 a 6 átomos de carbono, $-CN$, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-N(R^9)_2$, $-N(R^4)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, y $-NR^4S(O)_2$;

cada R^9 se selecciona independientemente a partir de H, cicloalquilo de 3 a 8 átomos de carbono y alquilo de 1 a 8 átomos de carbono, y

cada p es independientemente 1, 2, 3, 4, 5 ó 6.

En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), R^1 es  ,  ,  ,  o  , mientras que en otras modalidades, R^1 es  ,  o  .

En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), cada R^3 se selecciona independientemente a partir de halógeno, $-OR^9$, alquilo de 1 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono y heteroarilo de 2 a 13 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono y heteroarilo de 2 a 13 átomos de carbono de R^3 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hidroxilo, $-OR^9$, alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno y cicloalquilo de 3 a 8 átomos de carbono.

En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), el arilo de 6 a 14 átomos de carbono de R^3 es fenilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, alquilo de 1 a 8 átomos de carbono, y alquilo de 1 a 8 átomos de carbono sustituido por halógeno.

En ciertas modalidades de los compuestos anteriormente

mencionados de la fórmula (I), el arilo de 6 a 14 átomos de carbono de R^3 es fenilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de flúor y alquilo de 1 a 8 átomos de carbono.

En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), R^2 es arilo de 6 a 14 átomos de carbono, o heteroarilo de 2 a 13 átomos de carbono, en donde el arilo de 6 a 14 átomos de carbono, y heteroarilo de 2 a 13 átomos de carbono de R^2 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-OC(O)R^9$, alcoxilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno y alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno.

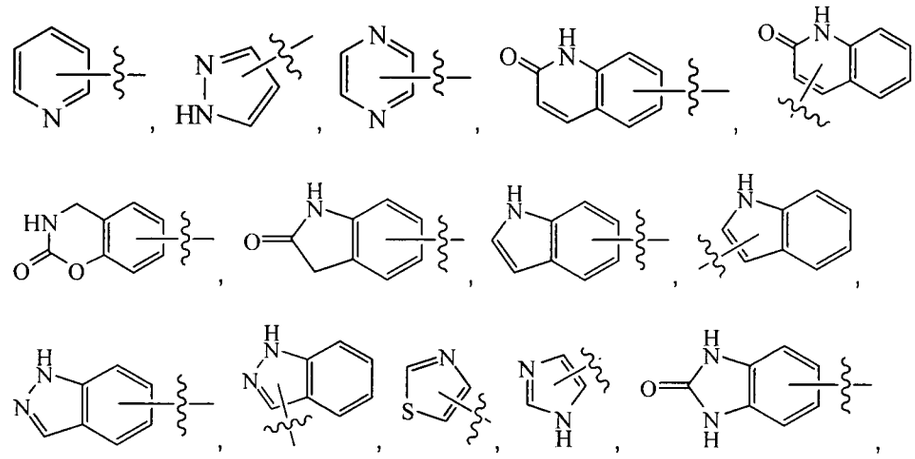
En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), R^2 es arilo de 6 a 14 átomos de carbono, o heteroarilo de 2 a 13 átomos de carbono, en donde el arilo de 6 a 14 átomos de carbono, y heteroarilo de 2 a 13 átomos de carbono de R^2 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de

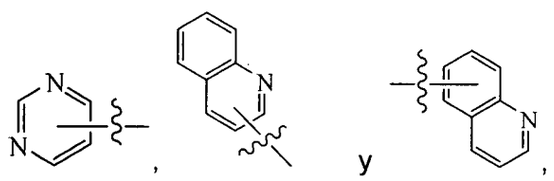
151

halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ y $-S(O)_2R^9$.

En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), el arilo de 6 a 14 átomos de carbono de R^2 es fenilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ y $-S(O)_2R^9$.

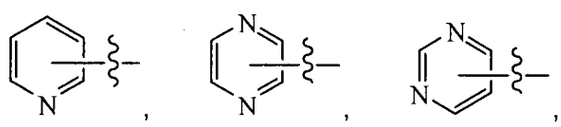
En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), el heteroarilo de 2 a 13 átomos de carbono de R^2 se selecciona a partir de:





en donde cada uno está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ y $-S(O)_2R^9$.

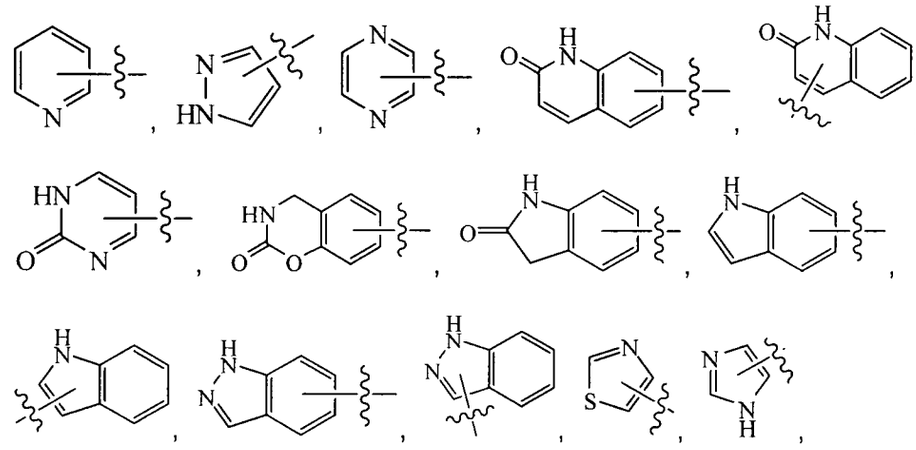
En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), el heteroarilo de 2 a 13 átomos de carbono de cada R^2 se selecciona a partir de:

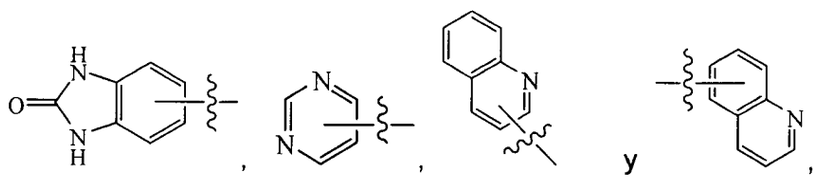


en donde cada uno está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ y $-S(O)_2R^9$.

En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), R^6 es heteroarilo de 2 a 13 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, -OCH $(R^7)_2$, alquilo de 1 a 8 átomos de carbono, o cicloalquilo de 3 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, y hetero-cicloalquilo de 2 a 14 átomos de carbono de R^6 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, –CN, $–OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-N(R^4)_2$, $–S(O)_2R^9$, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, alqueno de 2 a 8 átomos de carbono, y alquilo de 1 a 8 átomos de carbono sustituido por hidroxilo.

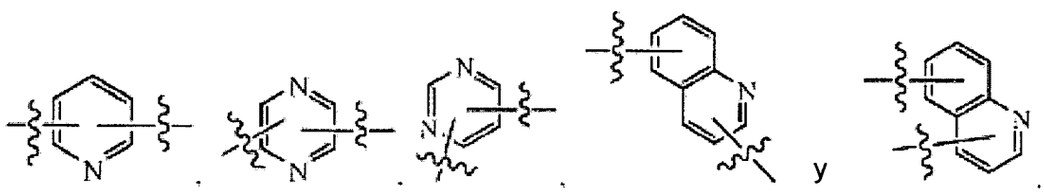
En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), R^6 se selecciona a partir de:





en donde cada uno está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, –CN, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-N(R^4)_2$, $-S(O)_2R^9$, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, alqueno de 2 a 8 átomos de carbono, y alquilo de 1 a 8 átomos de carbono sustituido por hidroxilo.

En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), Y^1 es arileno de 6 a 14 átomos de carbono o heteroarileno de 2 a 13 átomos de carbono, mientras que, en otras modalidades, Y^1 se selecciona a partir de:



En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), cada R^4 se selecciona independientemente a partir de H, alquilo de 1 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, $-L^1R^5$, $-L^1R^6$ y cicloalquilo de 3 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, arilo de

6 a 14 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, y cicloalquilo de 3 a 8 átomos de carbono están opcionalmente sustituidos con $-(CH_2)_pOR^9$.

En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), R^5 es arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, $-N(R^9)_2$, $-N(R^9)C(O)R^9$, $-(CH_2)_pOR^9$, u $-OR^9$.

En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), R^7 es $-L^1R^8$. En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), R^8 es $-N(R^9)_2$ o -CN.

En ciertas modalidades, los compuestos de la fórmula (I) se seleccionan a partir de:

(R)-1-(4-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-pirrolidin-3-ol; (R)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-piperidin-4-ol; 6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-indolin-2-ona; 3-(6-((3S)-2-(3-fluoro-fenil)-3-hidroxi-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 5-(6-(2-(2,5-dimetil-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-fluoro-benzonitrilo; (R)-4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 4-(5-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-morfolina; 4-(5-(6-(2-(3-fluoro-fenil)-

pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-morfolina; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-N-metil-picolinamida; 4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 5-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-N-metil-picolinamida; (S)-4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; (R)-4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 4-(5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-morfolina; 4-(6-(2-fenil-azetidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; (R)-4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; (S)-4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 4-(6-(2-(3-fluoro-fenil)-2-metil-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-3,4-dihidro-2H-benzo-[e][1,3]-oxazin-2-ona; 6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-3,4-dihidro-2H-benzo-[e][1,3]-oxazin-2-ona; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-indolin-2-ona; 6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-indolin-2-ona; 4-(6-(2-(2,5-difluoro-fenil)-5-metil-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 4-(2-(4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-1H-pirazol-1-il)-etil)-morfolina; N-(2-(4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-1H-

pirazol-1-il)-etil)-acetamida; (Z)-3-((1H-pirrol-2-il)-metilen)-6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-indolin-2-ona; 5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-fluoro-benzonitrilo; 5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-morfolino-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-fluoro-benzonitrilo; 5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(dimetil-amino)-benzonitrilo; 5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-metil-piperazin-1-il)-benzonitrilo; 5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-(2-metoxi-etil)-piperazin-1-il)-benzonitrilo; 5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-morfolino-etil-amino)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(dimetil-amino)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-metil-piperazin-1-il)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-(2-metoxi-etil)-piperazin-1-il)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-morfolino-etil-amino)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-morfolino-benzonitrilo; 3-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-morfolino-piperidin-1-il)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-

(pirrolidin-1-il)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(3-(dimetil-amino)-pirrolidin-1-il)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2,6-dimetil-morfolino)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-(pirrolidin-1-il)-etoxi)-benzonitrilo; 5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-nicotinonitrilo; 6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-picolinonitrilo; 4-(4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-tiazol-2-il)-morfolina; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(3-morfolino-propil-amino)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(3-morfolino-pirrolidin-1-il)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(1-metil-pirrolidin-3-iloxi)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-((2-(dimetil-amino)-etil)-(metil)-amino)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-((l-metil-pirrolidin-3-il)-metoxi)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(3-morfolino-propoxi)-benzonitrilo; 3-(5-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo; 4-(5-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo; 3-(5-(2-(2,5-difluoro-fenil)-tiazolidin-3-il)-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo; 3-(5-(2-(2,5-difluoro-fenil)-tiazolidin-3-il)-3H-imidazo-[4,5-b]-piridin-3-il)-

155

benzonitrilo; 3-(3-(1H-imidazol-2-il)-fenil)-5-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3H-imidazo-[4,5-b]-piridina; 3-(5-(2-(2,5-difluoro-fenil)-4-oxo-tiazolidin-3-il)-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo; 3-(5-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo; 4-(5-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo; 3-(6-(2-(3-fluoro-fenil)-3-oxo-pirazolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 5-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-hidroxi-piperidin-1-il)-benzonitrilo; 2-(1,3-bis-(dimetil-amino)-propan-2-iloxi)-4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(1-(dimetil-amino)-propan-2-iloxi)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-(1-metil-pirrolidin-2-il)-etoxi)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(3-(dimetil-amino)-2-hidroxi-propoxi)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-((1-metil-pirrolidin-2-il)-metoxi)-benzonitrilo; 4-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 3-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 2-(2-(dietil-amino)-etil-amino)-4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 7-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-oxo-1,2-dihidro-quinolin-3-carbonitrilo; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-morfolino-benzonitrilo; 5-(6-(2-(3-fluoro-fenil)-

pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-metil-piperazin-1-il)-benzonitrilo; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-(2-metoxi-etil)-piperazin-1-il)-benzonitrilo; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-morfolino-etil-amino)-benzonitrilo; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-morfolino-piperidin-1-il)-benzonitrilo; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-(pirrolidin-1-il)-etoxi)-benzonitrilo; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-(1-metil-pirrolidin-2-il)-etoxi)-benzonitrilo; 4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-metil-piperazin-1-il)-benzonitrilo; 4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-(pirrolidin-1-il)-etoxi)-benzonitrilo; 4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-morfolino-etoxi)-benzonitrilo; (R)-3-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; (S)-3-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 4-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; (R)-4-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; (S)-4-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; ácido 6-(6-(2-(2,5-dimetil-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-picolínico; 3-(6-((2R,4S)-3,3-difluoro-4-metil-2-fenil-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 3-(6-(2-fenil-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 6-(6-(2-fenil-pirrolidin-1-il)-

imidazo-[1,2-b]-piridazin-3-il)-3,4-dihidro-2H-benzo-[e][1,3]-oxazin-2-ona; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-((R)-pirrolidin-2-il-metoxi)-benzonitrilo; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-((S)-pirrolidin-2-il-metoxi)-benzonitrilo; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-(2-morfolino-2-oxo-etil)-piperazin-1-il)-benzonitrilo; 2-(4-(2-ciano-4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-fenil)-piperazin-1-il)-N,N-dimetil-acetamida; 2-(4-(3-(dimetil-amino)-propil)-piperazin-1-il)-5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-hidroxi-piperidin-1-il)-benzonitrilo; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-(4-isopropil-piperazin-1-il)-etoxi)-benzonitrilo; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-(4-(2-hidroxi-etil)-piperazin-1-il)-etoxi)-benzonitrilo; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(((R)-5-oxo-pirrolidin-2-il)-metoxi)-benzonitrilo; 3-(6-((2R,4S)-3,3-difluoro-2-(3-fluoro-fenil)-4-metil-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(1H-indol-4-il)-imidazo-[1,2-b]-piridazina; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(1-metil-1H-indol-2-il)-imidazo-[1,2-b]-piridazina; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(1H-indol-5-il)-imidazo-[1,2-b]-piridazina; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(5-(4-metil-piperazin-1-il)-pirazin-2-il)-imidazo-[1,2-b]-piridazina; 4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-

piridazin-3-il)-2-(piperidin-1-il)-tiazol; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(5-(pirrolidin-1-il)-pirazin-2-il)-imidazo-[1,2-b]-piridazina; 4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-carboxilato de terbutilo; 3-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-metil-fenil-carbamato de terbutilo; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(piridin-2-il)-imidazo-[1,2-b]-piridazina; 3-(6-cloro-pirazin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina; 3-(6-(1H-imidazol-1-il)-pirazin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina; 2-cloro-5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-tiazol; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-N,N-dimetil-pirazin-2-amina; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina; 4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-morfolina; (S)-6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-picolinonitrilo; (R)-6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-picolinonitrilo; 3-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-indolin-2-ona; 6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(1H-indol-4-il)-imidazo-[1,2-b]-piridazina; 4-(6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-morfolina; 6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(1H-indol-5-il)-imidazo-[1,2-b]-piridazina; (R)-4-(6-(3-(3-fluoro-fenil)-morfolino)-

imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; (S)-4-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(1H-indazol-5-il)-imidazo-[1,2-b]-piridazina; 3-(5-fluoro-6-metil-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina; 3-(3-fluoro-fenil)-4-(3-(piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina; 6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-nicotinonitrilo; 2-fluoro-5-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-metoxi-piridin-2-il)-imidazo-[1,2-b]-piridazina; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-fluoro-piridin-2-il)-imidazo-[1,2-b]-piridazina; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-N-(2-hidroxi-etil)-picolinamida; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-picolinamida; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(1H-indazol-6-il)-imidazo-[1,2-b]-piridazina; 6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(1H-indazol-6-il)-imidazo-[1,2-b]-piridazina; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(piperazin-1-il)-piridin-3-il)-imidazo-[1,2-b]-piridazina; 2-(4-(2-ciano-4-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-fenil)-piperazin-1-il)-N,N-dimetil-acetamida; 2-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il-amino)-etanol; 1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol; 6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(6-fluoro-piridin-2-il)-imidazo-[1,2-b]-piridazina; 4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-2-ona; 7-(6-(2-(3-

fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-oxo-1,2-dihidro-quinolin-3-carbonitrilo; 4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(piperazin-1-il-metil)-benzonitrilo; N1,N1-dietil-N2-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-etan-1,2-diamina; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(4-metil-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina; (2S)-3-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il-amino)-propano-1,2-diol; 6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(6-(piperazin-1-il)-piridin-3-il)-imidazo-[1,2-b]-piridazina; 6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(6-(piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina; 6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(6-(4-metil-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina; 4-(6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-2-ona; (3S)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirrolidin-3-ol; (3R)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirrolidin-3-ol; (3S,4S)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirrolidin-3,4-diol; 3-(3-fluoro-fenil)-4-(3-(5-(morfolino-metil)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina; 4-((6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-3-il)-metil)-morfolina; 4-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-2-((4-metil-piperazin-1-il)-metil)-benzonitrilo; 1-(6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol; 3-(3-fluoro-fenil)-4-(3-(6-fluoro-piridin-2-il)-

imidazo-[1,2-b]-piridazin-6-il)-morfolina; (5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-(4-hidroxi-piperidin-1-il)-metanona; 3-(3-fluoro-fenil)-4-(3-(6-morfolino-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina; 3-(3-fluoro-fenil)-4-(3-(6-(piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina; 4-(6-(2-(2-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 3-(6-(2-(2-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 4-(4-(6-(2-(2-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-tiazol-2-il)-morfolina; 5-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-metil-piperazin-1-il)-benzonitrilo; 2-(4-acetil-piperazin-1-il)-5-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 5-(6-(2-(2-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-hidroxi-piperidin-1-il)-benzonitrilo; 1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol; N-(5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-pirazin-2-il)-ciclopropan-carboxamida; 4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-((4-metil-piperazin-1-il)-metil)-benzonitrilo; (2S)-4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-2-metil-morfolina; ácido 1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carboxílico; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-metoxi-tiazol; ácido 4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-tiazol-2-carboxílico; (4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-

piridazin-3-il)-tiazol-2-il)-metanol; 1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-3-ol; (3R)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N,N-dimetil-pirrolidin-3-amina; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(1-metil-1H-imidazol-2-il)-imidazo-[1,2-b]-piridazina; 5-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-2-(piperazin-1-il)-benzonitrilo; 4-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-carboxilato de terbutilo; 3-(3-fluoro-fenil)-4-(3-(6-(4-metil-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina; 4-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-2,6-dimetil-morfolina; 3-(3-fluoro-fenil)-4-(3-(6-(piperidin-4-iloxi)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina; 4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(piperazin-1-il-metil)-tiazol; 2,2'-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il-azan-di-il)-dietanol; 4-(2-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-iloxi)-etil)-morfolina; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(2-(pirrolidin-1-il)-etoxi)-piridin-2-il)-imidazo-[1,2-b]-piridazina; 4-((6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-metil)-morfolina; 4-((6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-metil)-2,6-dimetil-morfolina; 1-((6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-metil)-pirrolidin-3-ol; 4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-metoxi-tiazol; 4-(5-(6-(3-(3-fluoro-fenil)-

morfolino)-imidazo-[1,2-b]-piridazin-3-il)-2-oxo-2,3-dihidro-1H-benzo-[d]-imidazol-1-il)-piperidin-1-carboxilato de etilo; 6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-nicotinonitrilo; 5-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-1-(piperidin-4-il)-1H-benzo-[d]-imidazol-2(3H)-ona; 2-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-N,N-dimetil-acetamida; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(4-isopropil-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina; 2-(1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-il)-propan-2-ol; 4-(1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-il)-morfolina; 3-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-propano-nitrilo; 1-(6-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol; 2-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-N-isopropil-acetamida; (1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-il)-metanol; (1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-3-il)-metanol; 1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carbonitrilo; 2-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-etanol; (6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-metanol; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(5-metil-1H-

imidazol-2-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina; 6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-picolinamida; (R)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-fluoro-piridin-2-il)-imidazo-[1,2-b]-piridazina; (R)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol; (1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-il)-metanol; 2-(1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-il)-etanol; 1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-3-carboxamida; 1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carboxamida; 6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-ol; ácido 6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-picolínico; 2-fluoro-3-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-quinolina; 3-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-quinolin-2(1H)-ona; 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-quinolina; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(4-(metil-sulfonil)-fenil)-imidazo-[1,2-b]-piridazina; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(piperidin-4-iloxi)-piridin-2-il)-imidazo-[1,2-b]-piridazina; (1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il-amino)-ciclopentil)-metanol; 3-(3-fluoro-fenil)-4-(3-(6-(4-(1-metil-piperidin-4-il)-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina; 3-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-quinolina; (6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-

imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-(4-hidroxi-piperidin-1-il)-metanona; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(2-fluoro-piridin-4-il)-imidazo-[1,2-b]-piridazina; 1-(4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol; N1,N1-dietil-N2-(6-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-etan-1,2-diamina; 6-(2-(3-fluoro-fenil)-piperidin-1-il)-3-(6-(4-isopropil-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina; (3S)-1-(6-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N,N-dimetil-pirrolidin-3-amina; 4-(3-(6-(2,5-diazabiciclo-[2.2.1]-heptan-2-il)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-3-(3-fluoro-fenil)-morfolina; 6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-N-(2-(piperazin-1-il)-etil)-piridin-2-amina; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(1-(metil-sulfonil)-piperidin-4-iloxi)-piridin-2-il)-imidazo-[1,2-b]-piridazina; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-a]-piridin-3-il)-2-fluoro-benzonitrilo; 2-etoxi-4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-a]-piridin-3-il)-tiazol; 5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-a]-piridin-3-il)-2-fluoro-benzonitrilo; ácido 4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-picolínico; ácido 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-picolínico; (2S,6R)-4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-2,6-dimetil-morfolina; 4-(6-(6-(2-(piridin-2-il)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-morfolina; 1-(6-(6-(2-(piridin-2-il)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol; 1-(6-(6-(2-(piridin-3-il)-

pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol; 6-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-N-metil-piridin-2-amina; 6-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-N-isopropil-piridin-2-amina; N-(6-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-metan-sulfonamida; 6-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-N,N-dimetil-piridin-2-amina; 6-(2-(3-fluoro-fenil)-piperidin-1-il)-3-(6-(piperidin-4-iloxi)-piridin-2-il)-imidazo-[1,2-b]-piridazina; ácido 1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-azetidin-3-carboxílico; 1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-azetidin-3-ol; 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-a]-piridin-3-il)-2-etoxi-tiazol; 1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol; (6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-metanol; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(5-metil-1H-imidazol-2-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina; (1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-il)-metanol; 2-(4-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-etanol; 1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-3-carboxamida; 1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carboxamida; 3-(3-fluoro-fenil)-4-(3-(6-(4-(1-metil-piperidin-4-il)-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina; 4-(3-(6-(2,5-diazabiciclo-[2.2.1]-

heptan-2-il)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-3-(3-fluoro-fenil)-morfolina; 6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-N-(2-(piperazin-1-il)-etil)-piridin-2-amina; 1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N-metil-piperidin-4-carboxamida; 1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N-(2-hidroxi-etil)-piperidin-4-carboxamida; (S)-6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-indolin-2-ona; (R)-6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-indolin-2-ona; (S)-1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol; (R)-1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol; 1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carboxilato de etilo; 3-(6-(1,3-dioxolan-2-il)-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina; ácido 1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carboxílico; 5-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-oxazol; 3-(3-fluoro-fenil)-4-(3-(6-(4-(3-isopropil-1,2,4-oxadiazol-5-il)-piperidin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina; N-(ciclopropil-metoxi)-1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carboxamida; 1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N-isopropil-piperidin-4-carboxamida; N-ciclopropil-1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carboxamida; 1-

(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N-(isoxazol-3-il)-piperidin-4-carboxamida; (1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-il)-(3-hidroxi-pirrolidin-1-il)-metanona; N-(ciano-metil)-1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carboxamida; 2-(1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-il)-etanol; 3-(6-(1H-pirazol-5-il)-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina; 5-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirazolo-[1,5-a]-pirimidin-2-carbonitrilo; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(2-metil-pirimidin-4-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina; 4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-amina; 3-(6-((2R,5S)-2,5-dimetil-piperazin-1-il)-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina; 3-(6-((3S,5R)-3,5-dimetil-piperazin-1-il)-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina; 6-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2(1H)-ona; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(4-(pirazin-2-il)-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(4-(pirimidin-2-il)-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(3-(piperidin-4-il)-1H-pirazol-5-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina; 4-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-morfolina; 6-(2-(3-

fluoro-fenil)-pirrolidin-1-il)-3-(6-(4-(2-(metil-sulfonil)-etil)-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina; 2-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il-amino)-etanol; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(6-(piperidin-4-il)-pirimidin-4-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina; 2-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-N,N-dimetil-etanamina; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(pirimidin-4-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina; 4-(1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirrolidin-3-il)-morfolina; 3-(6-(4-(ciclopropil-sulfonil)-piperazin-1-il)-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina; 1-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-2-hidroxi-etanona; (4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-(1-hidroxi-ciclopropil)-metanona; (R)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(2-metil-pirimidin-4-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina; (4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-(tetrahidro-2H-piran-4-il)-metanona; (4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-(tetrahidrofuran-2-il)-metanona; 4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,3'-bipiridin-6'-il)-morfolina; 6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(5-(pirrolidin-1-il)-pirazin-2-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina; 4-(5-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-

il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-morfolina; 1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-piperidin-4-ol; N1-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-N2,N2-dimetil-etan-1,2-diamina; 1-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-piperidin-4-ol; 4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N,N-dimetil-pirimidin-2-amina; 3-(6-(1H-indazol-5-il)-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina; 2-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,3'-bipiridin-6'-il-amino)-etanol; 1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,3'-bipiridin-6'-il)-piperidin-4-ol; (R)-2-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il-amino)-etanol; 4-((S)-1-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirrolidin-3-il)-morfolina; (2S,6R)-4-((S)-1-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirrolidin-3-il)-2,6-dimetil-morfolina; (R)-1-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-azetidin-3-ol; (R)-N-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-metan-sulfonamida; (R)-4-((S)-1-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirrolidin-3-il)-2-metil-morfolina; (R)-2-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il-amino)-

etanol; (R)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-azetidin-3-ol; (R)-1-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-pirrolidin-3-ol; (R)-N-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-metan-sulfonamida; (R)-4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N-(piridin-3-il-metil)-pirimidin-2-amina; (S)-1-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-N-metil-pirrolidin-3-amina; (R)-4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N-(2-(metil-sulfonil)-etil)-pirimidin-2-amina; (R)-N-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,3'-bipiridin-6'-il)-metan-sulfonamida; (R)-3-(6-(1H-indazol-6-il)-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina; (R)-1-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-N-metil-pirrolidin-3-amina; (R)-1-(6'-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,2'-bipiridin-6-il)-piperidin-4-ol; (R)-2-(6'-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,2'-bipiridin-6-il-amino)-etanol; (R)-1-(6'-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,2'-bipiridin-6-il)-N-metil-pirrolidin-3-amina; (R)-1-(4-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-N-metil-pirrolidin-3-amina; (R)-2-(4-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-piperazin-1-il)-etanol; (R)-2-(4-(6-(6-(2-(3-

fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-piperazin-1-il)-etanol; 1-((2S,6R)-4-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-2,6-dimetil-piperazin-1-il)-2-hidroxi-etanona; (R)-1-(6'-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,2'-bipiridin-6-il)-pirrolidin-3-ol; (R)-2-(4-(6'-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,2'-bipiridin-6-il)-piperazin-1-il)-etanol; (R)-4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-bencen-sulfonamida; (R)-3-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-bencen-sulfonamida; (R)-N-(6'-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,2'-bipiridin-6-il)-metan-sulfonamida; (R)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(2'-(piperazin-1-il)-2,4'-bipiridin-6-il)-imidazo-[1,2-b]-piridazina; (R)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(4-(metil-sulfonil)-fenil)-piridin-2-il)-imidazo-[1,2-b]-piridazina; (R)-4-(2-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-1H-pirazol-1-il)-etil)-morfolina; (R)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(2'-(4-isopropil-piperazin-1-il)-2,4'-bipiridin-6-il)-imidazo-[1,2-b]-piridazina; (R)-4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N-metil-bencen-sulfonamida; (S)-1-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-pirrolidin-3-ol; 2-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-(piperidin-4-iloxi)-piridina; {1-[(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-amino]-

ciclopentil}-metanol; (3S,4S)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3,4-diol; 1-{6-[6-(3-fenil-tiomorfolin-4-il)-imidazo-[1,2-b]-piridazin-3-il]-piridin-2-il}-piperidin-4-ol; 2-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-[(1-metan-sulfonil-piperidin-4-il)-oxi]-piridina; (3S,4S)-1-(6-{6-[(2S)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3,4-diol; (3S,4S)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3,4-diol; 4-(4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-1H-pirazol-1-il)-piperidina; N-[(3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-N-metil-metan-sulfonamida; 2-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-(3-fluoro-piperidin-1-il)-piridina; N-[(3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-N-metil-acetamida; N-[(3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-2-hidroxi-N-metil-acetamida; 2-(3,3-difluoro-piperidin-1-il)-6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridina; N-etil-N-[(3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-acetamida; N-etil-N-[(3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-2-hidroxi-acetamida; N-[(3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-metan-sulfonamida; N-[1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-

b]-piridazin-3-il}-piridin-2-il)-piperidin-4-il]-N-metil-metan-sulfonamida; N-[1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-il]-acetamida; 1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-3-metil-piperidin-4-ol; 1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-amina; 2,2,2-trifluoro-N-[(3S)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-acetamida; N-[(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-metan-sulfonamida; N-etil-N-[(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-acetamida; N-[1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-il]-N-metil-metan-sulfonamida; (3S)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-amina; 2-(dimetil-amino)-1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-etan-1-ona; (3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-3-metil-piperazina; acetato de 2-[(2R)-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-2-metil-piperazin-1-il]-2-oxoetilo; 1-[(2R)-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-2-metil-piperazin-1-il]-2-hidroxi-etan-1-ona; 2-amino-1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-

piperazin-1-il]-etan-1-ona; 1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-2-(metil-amino)-etan-1-ona; 2-(dimetil-amino)-1-[(2R)-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-2-metil-piperazin-1-il]-etan-1-ona; (3R)-3-{[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-carbonil}-morfolina; (3R)-3-{[(2R)-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-2-metil-piperazin-1-il]-carbonil}-morfolina; 8-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-octahidro-piperazino-[2,1-c]-morfolin-4-ona; (3R,4R)-1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piridin-2-il]-pirrolidin-3,4-diol; 1-(6-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-ol; 6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-carboxamida; 6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-ol; ácido 6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-carboxílico; 2-fluoro-3-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-quinolina; 3-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-1,2-dihidro-quinolin-2-ona; 5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-quinolina; 2-(3-fluoro-fenil)-1-[3-(4-metan-sulfonil-fenil)-imidazo-[1,2-b]-piridazin-6-il]-pirrolidina; 3-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-quinolina; 1-[(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-

imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-carbonil]-piperidin-4-ol; 2-fluoro-4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridina; 1-(4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-ol; 1-(4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-metil-piperazina; 2-[(4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-amino]-etan-1-ol; (3R)-1-[(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-carbonil]-N,N-dimetil-pirrolidin-3-amina; 1-(5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirimidin-2-il)-piperidin-4-ol; 6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-N-metil-piridin-2-carboxamida; 4-[(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-carbonil]-morfolina; (3R)-1-(4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-ol; (3S)-1-(4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-ol; (3R,4R)-1-(4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3,4-diol; 1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N,N-dimetil-piperidin-4-amina; 2-[(5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirimidin-2-il)-amino]-etan-1-ol; 5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-N-metil-pirimidin-2-amina; 5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-N,N-dimetil-pirimidin-2-amina; 1-(4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-

piridazin-3-il}-piridin-2-il)-N,N-dimetil-piperidin-4-amina; 2-cloro-5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirimidina; 4-[(5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo; 5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-2-(piperidin-4-iloxi)-pirimidina; 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N,N-dimetil-piperidin-4-amina; 5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirimidina; 5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-1,2-dihidro-pirimidina; 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-ona; 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazina; 6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-N-[1-(propan-2-il)-piperidin-4-il]-piridin-2-amina; carbamato de [1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-il]; N-metil-carbamato de 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-ilo; N-terbutil-carbamato de 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-ilo; 1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-etan-1-ona; N,N-dietil-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-amina; 2,2,2-trifluoro-1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-

il}-piridin-2-il)-piperazin-1-il]-etan-1-ona; 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-metan-sulfonil-piperazina; 2-(benciloxi)-1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-etan-1-ona; 1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-2-hidroxi-etan-1-ona; 2-{[1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-il]-amino}etan-1-ol; 2-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-(1,2,3,6-tetrahidro-piridin-1-il)-piridina; N,N-dietil-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-amina; N-ciclopropil-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-amina; (3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-metil-pirrolidin-3-amina; (3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-metil-pirrolidin-3-amina; 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-metil-piperidin-4-amina; 2-fluoro-N-[1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-N,2-dimetil-propanamida; 2-fluoro-N-[1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-N-metil-propanamida; 1-terbutil-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazina; ácido 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-

pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-carboxílico; 2-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-[4-(pirrolidin-1-il)-piperidin-1-il]-piridina; 2-fluoro-N-[1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-il]-N,2-dimetil-propanamida; 2,2,2-trifluoro-N-[(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-N-metil-acetamida; 6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-N-metil-N-(piperidin-4-il)-piridin-2-amina; 2-fluoro-N-[(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-N,2-dimetil-propanamida; [1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-il]-metanol; (3R)-N-(2-fluoro-2-metil-propil)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-metil-pirrolidin-3-amina; 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-(propan-2-sulfonil)-piperazina; 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-[(2-metil-propan)-sulfonil]-piperazina; 1-(butan-2-sulfonil)-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazina; 1-(etan-sulfonil)-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazina; (3S)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-metil-pirrolidin-3-amina; (3S)-N-etil-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-

il)-pirrolidin-3-amina; (3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-(2,2,2-trifluoro-etil)-pirrolidin-3-amina; acetato de 2-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-2-oxo-etilo; acetato de {[(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-carbamoil}-metilo; N-[(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-2-hidroxi-acetamida; 4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-1-metil-piperazin-2-ona; 4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-1-(2-hidroxi-etil)-piperazin-2-ona; 2-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-[4-(piperidin-1-il)-piperidin-1-il]-piridina; {[1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-il]-metil}-dimetil-amina; 2-(4,4-dimetil-piperidin-1-il)-6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridina; 2-(3,3-dimetil-piperidin-1-il)-6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridina; ácido 4-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-benzoico; acetato de 1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-2-metil-1-oxo-propan-2-ilo; acetato de (2S)-1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-1-oxo-propan-2-ilo; 1-(6-{6-[(2R)-2-(3-

fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N,N-dimetil-piperidin-4-amina; N,N-dietil-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-sulfonamida; N-etil-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-metil-piperidin-4-amina; (2S)-1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-2-hidroxi-propan-1-ona; 1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-2-hidroxi-2-metil-propan-1-ona; 8-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-1,4-dioxa-8-aza-espiro-[4.5]-decano; 4-etil-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-ol; 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-(propan-2-il)-piperidin-4-ol; 4-etenil-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-ol; 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-metil-piperidin-4-ol; 2-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-{octahidro-pirrolo-[1,2-b]-piperazin-2-il}-piridina; 8-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-3-metil-1,3,8-triaza-espiro-[4.5]-decano-2,4-diona; acetato de (1S)-1-{[(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-carbamoil}-etilo; (2S)-N-[(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-

piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-2-hidroxi-propanamida; 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-3-(trifluoro-metil)-piperazina; 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-metil-piperidin-3-amina; 1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piridin-2-il]-N,N-dimetil-piperidin-4-amina; acetato de 2-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-2-(trifluoro-metil)-piperazin-1-il]-2-oxo-etilo; 1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-2-(trifluoro-metil)-piperazin-1-il]-2-hidroxi-etan-1-ona; 1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piridin-2-il]-N-metil-piperidin-4-amina; 4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piridin-2-ol; N-ciclobutil-6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-amina; N-ciclopropil-6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-amina; N-ciclopropil-1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piridin-2-il]-piperidin-4-amina; 1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piridin-2-il]-piperidin-4-ona; 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-(piridin-3-il)-piperazina; 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-(piridin-2-il)-piperazina; 1-(4-fluoro-fenil)-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-

imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazina; 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-(6-metil-piridin-2-il)-piperazina; 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-[5-(trifluoro-metil)-piridin-2-il]-piperazina; 2-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-N-metil-N-fenil-acetamida; ácido 2-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-2-oxo-acético; 6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-carboxamida; 6-{6-[(2S)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-carboxamida; 2-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-etan-1-ol; 2-[4-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-N-(propan-2-il)-acetamida; [1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-il]-metanol; [1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-3-il]-metanol; 1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-carbonitrilo; 2-[4-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-etan-1-ol; 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-ol; 2-fluoro-6-{6-[(2S)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridina; 2-fluoro-6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-

piridazin-3-il}-piridina; dietil-({2-[(6-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-amino]-etil})-amina; 1-(6-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-(propan-2-il)-piperazina; (3S)-1-(6-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N,N-dimetil-pirrolidin-3-amina; 6-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-N-metil-piridin-2-amina; 6-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-N-(propan-2-il)-piridin-2-amina; N-(6-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-metan-sulfonamida; 6-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-N,N-dimetil-piridin-2-amina; 2-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-(piperidin-4-iloxi)-piridina; 1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-ol; (3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N,N-dimetil-pirrolidin-3-amina; 1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-(2-hidroxi-etil)-piperidin-4-carboxamida; N-[2-(dimetil-amino)-etil]-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-carboxamida; ácido 1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-carboxílico; N-(ciano-metil)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-carboxamida; 2-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirazina; N-[(3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-

170

[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-acetamida; 1-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-1H-pirazol; 1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirazin-2-il)-piperidin-4-ol; (3S)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirazin-2-il)-N,N-dimetil-pirrolidin-3-amina; 2-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-(piperazin-1-il)-pirazina; 2-[4-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirazin-2-il)-piperazin-1-il]-etan-1-ol; (3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirazin-2-il)-N,N-dimetil-pirrolidin-3-amina; N-[1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-il]-acetamida; 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-amina; N-[1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-il]-metan-sulfonamida; N-etil-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-amina; N,N-dietil-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-amina; 3-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-1H-pirrol; N-[1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-il]-2-hidroxi-acetamida; N-etil-N-[1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-il]-metan-sulfonamida; 1-[6-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-

piridin-2-il]-piperidin-4-ol; 6-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-2-oxa-6-aza-espiro-[3.3]-heptano; 6-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirimidin-2-il]-2-oxa-6-aza-espiro-[3.3]-heptano; 6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-2,3-dihidro-1H-indol-2-ona; 6-{6-[3-(3-fluoro-fenil)-morfolin-4-il]-imidazo-[1,2-b]-piridazin-3-il}-2,3-dihidro-1H-indol-2-ona; 3-(3-fluoro-fenil)-4-{3-[6-(piperazin-1-il)-piridin-2-il]-imidazo-[1,2-b]-piridazin-6-il}-morfolina; (3S)-4-[3-(6-fluoro-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il]-3-fenil-morfolina; 1-(6-{6-[(3S)-3-fenil-morfolin-4-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-ol; 1-(6-{6-[3-(3-fluoro-fenil)-morfolin-4-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-carbaldehído; 3-(3-fluoro-fenil)-4-(3-{6-[4-(4-metil-1H-imidazol-2-il)-piperidin-1-il]-piridin-2-il}-imidazo-[1,2-b]-piridazin-6-il)-morfolina; 6-{6-[3-(3-fluoro-fenil)-morfolin-4-il]-imidazo-[1,2-b]-piridazin-3-il}-N,N-dimetil-piridin-2-amina; 3-(3-fluoro-fenil)-4-[3-(6-{4-[2-(metil-sulfanil)-etil]-piperazin-1-il}-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il]-morfolina; 3-(3-fluoro-fenil)-4-(3-{6-[4-(2-metan-sulfonil-etil)-piperazin-1-il]-piridin-2-il}-imidazo-[1,2-b]-piridazin-6-il)-morfolina; (N-ciclopropil-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-piperidin-4-amina); 3-(3-fluoro-fenil)-4-(3-{6-[4-(1H-1,2,4-triazol-5-il)-piperidin-1-il]-piridin-2-il}-imidazo-[1,2-b]-piridazin-6-il)-morfolina, y 3-(3-fluoro-fenil)-4-(3-{6-[4-(1,2,4-oxadiazol-5-il)-piperidin-1-il]-piridin-2-il}-imidazo-[1,2-b]-piridazin-6-il)-morfolina.

Otro aspecto proporcionado en la presente es el de las composiciones farmacéuticas que comprenden una cantidad terapéuticamente efectiva de un compuesto de la fórmula (I), y un vehículo farmacéuticamente aceptable.

En ciertas modalidades de estas composiciones farmacéuticas, las composiciones farmacéuticas se formulan para administración intravenosa, administración oral, administración rectal, inhalación, administración nasal, administración tópica, administración oftálmica, o administración ótica. En ciertas modalidades de estas composiciones farmacéuticas, la composición farmacéutica es una tableta, una píldora, una cápsula, un líquido, un inhalante, una solución de aspersión nasal, un supositorio, una solución, una emulsión, un ungüento, gotas para los ojos, o gotas para los oídos.

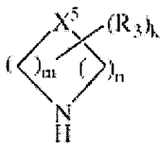
Otro aspecto proporcionado en la presente es el de los medicamentos para el tratamiento de una enfermedad o condición mediada por cinasa en un paciente, en donde el medicamento comprende una cantidad terapéuticamente efectiva de un compuesto de la fórmula (I), en donde la cinasa se selecciona a partir de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y ALK.

Otro aspecto proporcionado en la presente es el uso de un compuesto de la fórmula (I) en la elaboración de un medicamento para el tratamiento de una enfermedad o condición mediada por cinasa, en donde la cinasa se selecciona a partir de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB,

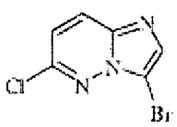
TrkC, IGF-1R, ALK4, ALK5 y ALK.

Otro aspecto proporcionado en la presente es un método para la elaboración de cualquiera de los compuestos anteriormente mencionados de la fórmula (I), en donde X^1 es N; X^2 es N; X^3 es C, y X^4 es C. Este método comprende:

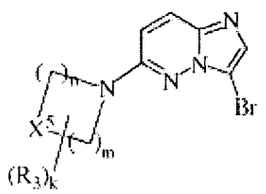
Mezclar un compuesto de la estructura:



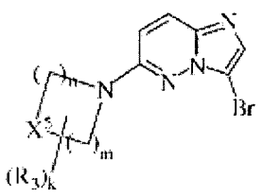
con un compuesto que tiene la estructura:



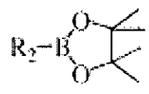
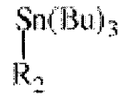
en la presencia de KF, para proporcionar un compuesto que tiene la estructura:



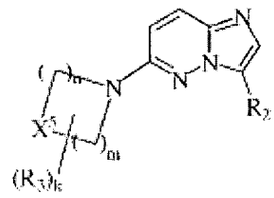
y mezclar, en la presencia de un catalizador de paladio, el compuesto que tiene la estructura:



con un compuesto que tiene ya sea la estructura:

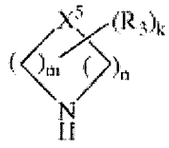
R^2-$B(OH)_2$,  , o bien,  ,

para proporcionar un compuesto que tiene la estructura:

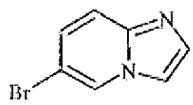


Otro aspecto proporcionado en la presente es un método para la elaboración de cualquiera de los compuestos anteriormente mencionados de la fórmula (I), en donde X^1 es CR^9; X^2 es N; X^3 es C, y X^4 es C. Este método comprende:

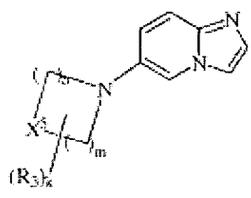
Mezclar un compuesto de la estructura:



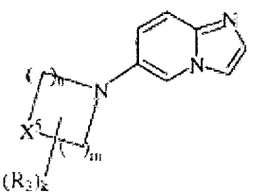
con un compuesto que tiene la estructura:



en la presencia de un catalizador de paladio, para proporcionar un compuesto que tiene la estructura:



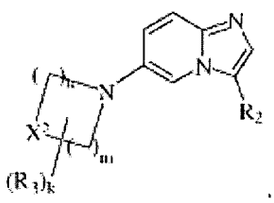
y mezclar, en la presencia de un catalizador de paladio, el compuesto que tiene la estructura:



con un compuesto que tiene la estructura:

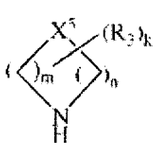
R^2-Br,

para proporcionar un compuesto que tiene la estructura:

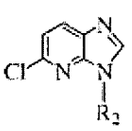


Otro aspecto proporcionado en la presente es un método para la elaboración de cualquiera de los compuestos anteriormente mencionados de la fórmula (I), en donde X^1 es N; X^2 es C; X^3 es N, y X^4 es C. Este método comprende:

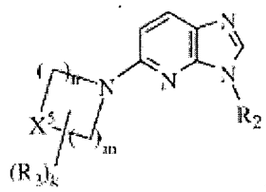
Mezclar un compuesto de la estructura:



con un compuesto que tiene la estructura:



en la presencia de un catalizador de paladio, para proporcionar un compuesto que tiene la estructura:



Otro aspecto proporcionado en la presente es el de los métodos para inhibir una cinasa, los cuales comprenden administrar a un sistema o a un sujeto que lo necesite, una cantidad terapéuticamente efectiva de un compuesto de la fórmula (I), o sales farmacéuticamente aceptables o composiciones farmacéuticas del mismo, inhibiendo de esta manera la cinasa. En ciertas modalidades de estos métodos, la cinasa se selecciona a partir de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y ALK, o una combinación de las mismas. En ciertas modalidades de estos métodos, la cinasa es TrkA, TrkB, TrkC o ALK. En ciertas modalidades de estos métodos, el método comprende administrar el compuesto a una célula o a un sistema de tejidos o a un sujeto humano o animal.

Otro aspecto proporcionado en la presente es el de los métodos para el tratamiento de una enfermedad o condición mediada por cinasa, los cuales comprenden administrar a un sistema o a un sujeto que necesite dicho tratamiento, una cantidad efectiva de un compuesto de la fórmula (I), o sales farmacéuticamente aceptables o composiciones farmacéuticas del mismo, tratando de esta manera la

condición, y en donde la cinasa se selecciona a partir de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y ALK, o una combinación de las mismas. En ciertas modalidades de estos métodos, el método comprende administrar el compuesto a una célula o a un sistema de tejidos; o a un sujeto humano o animal. En ciertas modalidades de estos métodos, la enfermedad o condición es cáncer, una enfermedad proliferativa, un trastorno de dolor, una enfermedad dermatológica, una enfermedad metabólica, una enfermedad muscular, una enfermedad neurodegenerativa, una enfermedad neurológica, una enfermedad de inmunodeficiencia, una enfermedad inmunológicamente mediada, una enfermedad autoinmune, una enfermedad auto-inmunológicamente mediada, una enfermedad ósea, una enfermedad inflamatoria, fibrosis, una enfermedad oftálmica, una enfermedad infecciosa, una enfermedad viral, reparación de heridas, una enfermedad respiratoria, una enfermedad pulmonar, una enfermedad renal, una enfermedad del riñón, una enfermedad hepática, una enfermedad cardiovascular, una enfermedad vascular, una enfermedad cardíaca, muerte celular, y una enfermedad inflamatoria por hiperplasia. En ciertas modalidades de estos métodos, la enfermedad o condición es asma, enfermedad pulmonar obstructiva crónica (COPD), síndrome de insuficiencia respiratoria de adultos (ARDS), colitis ulcerativa, enfermedad de Crohn, bronquitis, dermatitis, rinitis alérgica, soriasis, esclerodermia, urticaria, artritis reumatoide, esclerosis múltiple, linfoma, metástasis, linfoma

macrocelular anaplásico, osteosarcoma, fibrosarcoma, melanoma, cáncer de mama, cáncer renal, cáncer de cerebro, cáncer de próstata, cáncer colo-rectal, cáncer de tiroides, cáncer de ovario, cáncer pancreático, cáncer neuronal, neuroblastoma, cáncer de pulmón, cáncer uterino, cáncer gastrointestinal, VIH, o lupus.

Otro aspecto proporcionado en la presente es el de los métodos para el tratamiento de una condición proliferativa celular, los cuales comprenden administrar a un sistema o a un sujeto que necesite dicho tratamiento, una cantidad efectiva de un compuesto de la fórmula (I), o sales farmacéuticamente aceptables o composiciones farmacéuticas del mismo; en donde la condición proliferativa celular es linfoma, metástasis, linfoma macrocelular anaplásico, osteosarcoma, fibrosarcoma, melanoma, cáncer de mama, cáncer renal, cáncer de cerebro, cáncer de próstata, cáncer colo-rectal, cáncer de tiroides, cáncer de ovario, cáncer pancreático, cáncer neuronal, neuroblastoma, cáncer de pulmón, cáncer uterino o cáncer gastrointestinal. En ciertas modalidades de estos métodos, la condición proliferativa celular es linfoma macrocelular anaplásico, cáncer pancreático, cáncer de ovario y cáncer de pulmón.

Otro aspecto proporcionado en la presente es el de los compuestos para utilizarse en un método de tratamiento médico, en donde el método de tratamiento médico es para el tratamiento de una enfermedad seleccionada a partir de cáncer, una enfermedad proliferativa, un trastorno de dolor, una enfermedad dermatológica, una enfermedad metabólica, una enfermedad muscular, una

enfermedad neurodegenerativa, una enfermedad neurológica, una enfermedad de inmunodeficiencia, una enfermedad inmunológicamente mediada, una enfermedad autoinmune, una enfermedad auto-inmunológicamente mediada, una enfermedad ósea, una enfermedad inflamatoria, fibrosis, una enfermedad oftálmica, una enfermedad infecciosa, una enfermedad viral, reparación de heridas, una enfermedad respiratoria, una enfermedad pulmonar, una enfermedad renal, una enfermedad del riñón, una enfermedad hepática, una enfermedad cardiovascular, una enfermedad vascular, una enfermedad cardíaca, una enfermedad inflamatoria por muerte celular e hiperplasia, y en donde el compuesto es un compuesto de la fórmula (I). En ciertas modalidades, la enfermedad es asma, enfermedad pulmonar obstructiva crónica (COPD), síndrome de insuficiencia respiratoria de adultos (ARDS), colitis ulcerativa, enfermedad de Crohn, bronquitis, dermatitis, rinitis alérgica, soriasis, esclerodermia, urticaria, artritis reumatoide, esclerosis múltiple, linfoma, metástasis, linfoma macrocelular anaplásico, osteosarcoma, fibrosarcoma, melanoma, cáncer de mama, cáncer renal, cáncer de cerebro, cáncer de próstata, cáncer colo-rectal, cáncer de tiroides, cáncer de ovario, cáncer pancreático, cáncer neuronal, neuroblastoma, cáncer de pulmón, cáncer uterino, cáncer gastrointestinal, VIH, o lupus.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Definiciones

Los términos "alquenilo" y "alqueno", como se utilizan en la

presente, se refieren a un hidrocarburo parcialmente insaturado de cadena ramificada o recta, que tiene cuando menos un doble enlace de carbono-carbono. Los átomos orientados alrededor del doble enlace están en la conformación ya sea *cis* (Z) o *trans* (E). Un grupo alquenilo o alqueno puede estar opcionalmente sustituido. Como se utilizan en la presente, los términos "alquenilo de 2 a 3 átomos de carbono", "alquenilo de 2 a 4 átomos de carbono", "alquenilo de 2 a 5 átomos de carbono", "alquenilo de 2 a 6 átomos de carbono", "alquenilo de 2 a 7 átomos de carbono", y "alquenilo de 2 a 8 átomos de carbono", se refieren a un grupo alquenilo que contiene cuando menos 2, y cuando mucho 3, 4, 5, 6, 7 u 8 átomos de carbono, respectivamente. Los ejemplos no limitantes de los grupos alquenilo, como se utilizan en la presente, incluyen etenilo, propenilo, butenilo, pentenilo, hexenilo, heptenilo, octenilo, nonenilo, decenilo, y similares. Como se utilizan en la presente, los términos "alqueno de 2 a 3 átomos de carbono", "alqueno de 2 a 4 átomos de carbono", "alqueno de 2 a 5 átomos de carbono", "alqueno de 2 a 6 átomos de carbono", "alqueno de 2 a 7 átomos de carbono", y "alqueno de 2 a 8 átomos de carbono", se refieren a un grupo alqueno que contiene cuando menos 2, y cuando mucho 3, 4, 5, 6, 7, u 8 átomos de carbono, respectivamente. Los ejemplos no limitantes de los grupos alqueno, como se utilizan en la presente, incluyen eteno, propeno, buteno, penteno, hexeno, hepteno, octeno, noneno, deceno, y similares.

El término "alquenileno", como se utiliza en la presente, se

refiere a un radical de hidrocarburo divalente parcialmente insaturado de cadena ramificada o recta derivado a partir de un grupo alquenilo. Un grupo alquenileno puede estar opcionalmente sustituido. Como se utilizan en la presente, los términos "alquenileno de 2 a 3 átomos de carbono", "alquenileno de 2 a 4 átomos de carbono", "alquenileno de 2 a 5 átomos de carbono", "alquenileno de 2 a 6 átomos de carbono", "alquenileno de 2 a 7 átomos de carbono", y "alquenileno de 2 a 8 átomos de carbono", se refieren a un grupo alquenileno que contiene cuando menos 2, y cuando mucho 3, 4, 5, 6, 7 u 8 átomos de carbono, respectivamente. Los ejemplos no limitantes de los grupos alquenileno, como se utilizan en la presente, incluyen, etenileno, propenileno, butenileno, pentenileno, hexenileno, heptenileno, octenileno, nonenileno, decenileno, y similares.

El término "alquilo", como se utiliza en la presente, se refiere a un hidrocarburo saturado de cadena ramificada o recta. Como se utiliza en la presente, los términos "alquilo de 1 a 3 átomos de carbono", "alquilo de 1 a 4 átomos de carbono", "alquilo de 1 a 5 átomos de carbono", "alquilo de 1 a 6 átomos de carbono", "alquilo de 1 a 7 átomos de carbono" y "alquilo de 1 a 8 átomos de carbono", se refieren a un grupo alquilo que contiene cuando menos 1, y cuando mucho 3, 4, 5, 6, 7 o 8 átomos de carbono, respectivamente. Los ejemplos no limitantes de los grupos alquilo, como se utilizan en la presente, incluyen metilo, etilo, propilo normal, isopropilo, butilo normal, isobutilo, butilo secundario, terbutilo, pentilo normal, isopentilo, hexilo, heptilo, octilo, nonilo, decilo y similares.

El término "alquileno", como se utiliza en la presente, se refiere a un radical de hidrocarburo divalente saturado de cadena ramificada o recta derivado a partir de un grupo alquilo. Un grupo alquileno puede estar opcionalmente sustituido. Como se utiliza en la presente, los términos "alquileno de 1 a 3 átomos de carbono", "alquileno de 1 a 4 átomos de carbono", "alquileno de 1 a 5 átomos de carbono", "alquileno de 1 a 6 átomos de carbono", "alquileno de 1 a 7 átomos de carbono", y "alquileno de 1 a 8 átomos de carbono", se refieren a un grupo alquileno que contiene cuando menos 1, y cuando mucho 3, 4, 5, 6, 7, u 8 átomos de carbono, respectivamente. Los ejemplos no limitantes de los grupos alquileno, como se utilizan en la presente, incluyen metileno, etileno, propileno normal, isopropileno, butileno normal, isobutileno, butileno secundario, butileno terciario, pentileno normal, isopentileno, hexileno, y similares.

El término "alquinilo", como se utiliza en la presente, se refiere a un radical de hidrocarburo parcialmente insaturado de cadena ramificada o recta, que tiene cuando menos un triple enlace de carbono-carbono. Un grupo alquinilo puede estar opcionalmente sustituido. Como se utilizan en la presente, los términos "alquinilo de 2 a 3 átomos de carbono", "alquinilo de 2 a 4 átomos de carbono", "alquinilo de 2 a 5 átomos de carbono", "alquinilo de 2 a 6 átomos de carbono", "alquinilo de 2 a 7 átomos de carbono", y "alquinilo de 2 a 8 átomos de carbono", se refieren a un grupo alquinilo que contiene cuando menos 2, y cuando mucho 3, 4, 5, 6, 7 u 8 átomos de

carbono, respectivamente. Los ejemplos no limitantes de los grupos alquinilo, como se utilizan en la presente, incluyen etinilo, propinilo, butinilo, pentinilo, hexinilo, heptinilo, octinilo, noninilo, decinilo y similares.

El término "alquinileno", como se utiliza en la presente, se refiere a un radical de hidrocarburo divalente parcialmente insaturado de cadena ramificada o recta derivado a partir de un grupo alquinilo. Un grupo alquinileno puede estar opcionalmente sustituido. Como se utilizan en la presente, los términos "alquinileno de 2 a 3 átomos de carbono", "alquinileno de 2 a 4 átomos de carbono", "alquinileno de 2 a 5 átomos de carbono", "alquinileno de 2 a 6 átomos de carbono", "alquinileno de 2 a 7 átomos de carbono", y "alquinileno de 2 a 8 átomos de carbono", se refieren a un grupo alquinileno que contiene cuando menos 2, y cuando mucho 3, 4, 5, 6, 7 u 8 átomos de carbono, respectivamente. Los ejemplos no limitantes de los grupos alquinileno, como se utilizan en la presente, incluyen, etinileno, propinileno, butinileno, pentinileno, hexinileno, heptinileno, octinileno, noninileno, decinileno, y similares.

El término "alcoxilo", como se utiliza en la presente, se refiere al grupo $-OR_a$, en donde R_a es un grupo alquilo como se define en la presente. Un grupo alcoxilo puede estar opcionalmente sustituido. Como se utilizan en la presente, los términos "alcoxilo de 1 a 3 átomos de carbono", "alcoxilo de 1 a 4 átomos de carbono", "alcoxilo de 1 a 5 átomos de carbono", "alcoxilo de 1 a 6 átomos de carbono", "alcoxilo de 1 a 7 átomos de carbono" y "alcoxilo de 1 a 8 átomos de

carbono", se refieren a un grupo alcoxilo en donde la fracción de alquilo contiene cuando menos 1, y cuando mucho 3, 4, 5, 6, 7 u 8 átomos de carbono. Los ejemplos no limitantes de los grupos alcoxilo, como se utilizan en la presente, incluyen metoxilo, etoxilo, propoxilo normal, isopropoxilo, butiloxilo normal, butiloxilo terciario, pentiloxilo, hexiloxilo, heptiloxilo, octiloxilo, noniloxilo, deciloxilo, y similares.

El término "arilo", como se utiliza en la presente, se refiere a los sistemas de anillos monocíclicos, bicíclicos, y tricíclicos que tienen un total de cinco a catorce miembros de anillo, en donde cuando menos un anillo en el sistema es aromático, y en donde cada anillo en el sistema contiene de 3 a 7 miembros del anillo. Un grupo arilo puede estar opcionalmente sustituido con uno o más sustituyentes. Los ejemplos no limitantes de los grupos arilo, como se utilizan en la presente, incluyen fenilo, naftilo, fluorenilo, indenilo, azulenilo, antracenilo, y similares.

El término "arileno,", como se utiliza en la presente, significa un radical divalente derivado a partir de un grupo arilo. Un grupo arileno puede estar opcionalmente sustituido.

El término "ciano", como se utiliza en la presente, se refiere a un grupo -CN.

El término "cicloalquilo", como se utiliza en la presente, se refiere a un ensamble de anillo monocíclico, bicíclico fusionado, tricíclico fusionado, o policíclico puenteado, saturado o parcialmente insaturado. Como se utiliza en la presente, los términos "cicloalquilo

de 3 a 5 átomos de carbono", "cicloalquilo de 3 a 6 átomos de carbono", "cicloalquilo de 3 a 7 átomos de carbono", "cicloalquilo de 3 a 8 átomos de carbono", "cicloalquilo de 3 a 9 átomos de carbono", y "cicloalquilo de 3 a 10 átomos de carbono" se refieren a un grupo cicloalquilo en donde el ensamble de anillo monocíclico, bicíclico fusionado, o policíclico puenteado, saturado o parcialmente insaturado contiene cuando menos 3, y cuando mucho 5, 6, 7, 8, 9 ó 10 átomos de carbono. Un grupo cicloalquilo puede estar opcionalmente sustituido. Los ejemplos no limitantes de los grupos cicloalquilo, como se utilizan en la presente, incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclo-octilo, ciclononilo, ciclodecilo, ciclopentenilo, ciclohexenilo, decahidro-naftalenilo, 2,3,4,5,6,7-hexahidro-1H-indenilo y similares.

El término "cicloalquileno", como se utiliza en la presente, significa un radical divalente derivado a partir de un grupo cicloalquilo. Un grupo cicloalquileno puede estar opcionalmente sustituido.

El término "halógeno", como se utiliza en la presente, se refiere a flúor (F), cloro (Cl), bromo (Br), o yodo (I).

El término "halo", como se utiliza en la presente, se refiere a los radicales de halógeno: flúor (-F), cloro (-Cl), bromo (-Br), y iodo (-I).

Los términos "halo-alquilo" o "alquilo sustituido por halógeno", como se utiliza en la presente, se refiere a un grupo alquilo como se define en la presente, sustituido con uno o más grupos halógeno, en

donde los grupos halógeno son iguales o diferentes. Un grupo halo-alquilo puede estar opcionalmente sustituido. Los ejemplos no limitantes de los grupos halo-alquilo de cadena ramificada o recta, como se utilizan en la presente, incluyen metilo, etilo, propilo, isopropilo, isobutilo, y butilo normal, sustituidos con uno o más grupos halógeno, en donde los grupos halógeno son iguales o diferentes, incluyendo, pero no limitándose a, trifluoro-metilo, pentafluoro-etilo, y similares.

Los términos "halo-alquenilo" o "alquenilo sustituido por halógeno", como se utilizan en la presente, se refieren a un grupo alquenilo como se define en la presente, sustituido con uno o más grupos halógeno, en donde los grupos halógeno son iguales o diferentes. Un grupo halo-alquenilo puede estar opcionalmente sustituido. Los ejemplos no limitantes de los grupos halo-alquenilo de cadena ramificada o recta, como se utilizan en la presente, incluyen etenilo, propenilo, butenilo, pentenilo, hexenilo, heptenilo, octenilo, nonenilo, decenilo, y similares, sustituidos con uno o más grupos halógeno, en donde los grupos halógeno son iguales o diferentes.

Los términos "halo-alquinilo" o "alquinilo sustituido por halógeno", como se utilizan en la presente, se refieren a un grupo alquinilo como se define anteriormente, sustituido con uno o más grupos halógeno, en donde los grupos halógeno son iguales o diferentes. Un grupo halo-alquinilo puede estar opcionalmente sustituido. Los ejemplos no limitantes de los grupos halo-alquinilo de

cadena ramificada o recta, como se utilizan en la presente, incluyen etinilo, propinilo, butinilo, pentinilo, hexinilo, heptinilo, octinilo, noninilo, decinilo, y similares, sustituidos con uno o más grupos halógeno, en donde los grupos halógeno son iguales o diferentes.

El término "halo-alcoxilo", como se utiliza en la presente, se refiere a un grupo alcoxilo como se define en la presente, sustituido con uno o más grupos halógeno, en donde los grupos halógeno son iguales o diferentes. Un grupo halo-alcoxilo puede estar opcionalmente sustituido. Los ejemplos no limitantes de los grupos halo-alcoxilo de cadena ramificada o recta, como se utilizan en la presente, incluyen metoxilo, etoxilo, propoxilo normal, isopropoxilo, butiloxilo normal, butiloxilo terciario, pentiloxilo, hexiloxilo, heptiloxilo, octiloxilo, noniloxilo, deciloxilo, y similares, sustituidos con uno o más grupos halógeno, en donde los grupos halógeno son iguales o diferentes.

El término "heteroalquilo", como se utiliza en la presente, se refiere a un grupo alquilo como se define en la presente, en donde uno o más átomos de carbono son independientemente reemplazados por uno o más de oxígeno, azufre, nitrógeno, o combinaciones de los mismos.

El término "heteroarilo", como se utiliza en la presente, se refiere a los sistemas de anillos monocíclicos, bicíclicos, y tricíclicos que tienen un total de cinco a catorce miembros del anillo, en donde cuando menos un anillo en el sistema es aromático, y cuando menos un anillo en el sistema contiene uno o más heteroátomos

seleccionados a partir de nitrógeno, oxígeno y azufre, y en donde cada anillo del sistema contiene de 3 a 7 miembros del anillo. Un grupo heteroarilo puede estar opcionalmente sustituido con uno o más sustituyentes. Los ejemplos no limitantes de los grupos heteroarilo, como se utilizan en la presente, incluyen benzo-furanilo, benzo-furazanilo, benzoxazolilo, benzo-piranilo, benzotiazolilo, benzo-tienilo, benzazepinilo, bencimidazolilo, benzo-tiopiranilo, benzo-[1,3]-dioxol, benzo-[b]-furilo, benzo-[b]-tienilo, 1H-benzo-[d]-imidazol-2(3H)-ona, benzo-[e][1,3]-oxazin-2-ona, cinolinilo, furazanilo, furilo, furopiridinilo, imidazolilo, indolilo, indolizinilo, indolin-2-ona, indazolilo, indolin-2-ona, isoindolilo, isoquinolinilo, isoxazolilo, isotiazolilo, 1,8-naftiridinilo, oxazolilo, oxaindolilo, oxadiazolilo, pirazolilo, pirrolilo, ftalazinilo, pteridinilo, purinilo, piridilo, piridazinilo, pirazinilo, pirimidinilo, quinoxalinilo, quinolinilo, quinazolinilo, 4H-quinolizinilo, quinolin-2(1H)-ona, tiazolilo, tiadiazolilo, tienilo, triazinilo, triazolilo, y tetrazolilo.

El término "hetero-arileno", como se utiliza en la presente, significa un radical divalente derivado a partir de un grupo heteroarilo. Un grupo hetero-arileno puede estar opcionalmente sustituido.

El término "hetero-cicloalquilo", como se utiliza en la presente, se refiere a un cicloalquilo, como se define en la presente, en donde uno o más de los átomos de carbono del anillo son reemplazados por una fracción seleccionada a partir de -O-, -N=, -NR-, -C(O)-, -S-, -S(O) - o -S(O)2-, en donde R es hidrógeno, alquilo de 1 a 4 átomos

de carbono, o un grupo protector de nitrógeno, con la condición de que el anillo de este grupo no contenga dos átomos de O o S adyacentes. Un grupo hetero-cicloalquilo puede estar opcionalmente sustituido. Los ejemplos no limitantes de los grupos hetero-cicloalquilo, como se utilizan en la presente, incluyen morfolino, pirrolidinilo, pirrolidinil-2-ona, piperazinilo, piperazinil-2-ona, piperidinilo, piperidinilona, 1,4-dioxa-8-aza-espiro-[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, tetrahidro-furanilo, dihidro-furanilo, tetrahidro-tienilo, tetrahidro-piranilo, dihidro-piranilo, tetrahidro-tiopiranilo, tioxanilo, azetidinilo, oxetanilo, tietanilo, oxepanilo, tiepanilo, 1,2,3,6-tetrahidro-piridinilo, 2H-piranilo, 4H-piranilo, dioxanilo, 1,3-dioxolanilo, ditianilo, ditiolanilo, dihidro-piranilo, dihidro-tienilo, dihidro-furanilo, imidazolinilo, imidazolidinilo, 3-azabiciclo-[3.1.0]-hexanilo, 2,5-diazabiciclo-[2.2.1]-heptano, y 3-azabiciclo-[4.1.0]-heptanilo.

El término "hetero-cicloalquileno", como se utiliza en la presente, significa un radical divalente derivado a partir de un grupo hetero-cicloalquilo. Un grupo hetero-cicloalquileno puede estar opcionalmente sustituido.

El término "heteroátomo", como se utiliza en la presente, se refiere a uno o más de oxígeno, azufre, nitrógeno, fósforo, o silicio.

El término "hidroxilo", como se utiliza en la presente, se refiere al grupo -OH.

El término "hidroxi-alquilo", como se utiliza en la presente, se refiere a un grupo alquilo como se define en la presente, sustituido con uno o más grupos hidroxilo. Los ejemplos no limitantes de los grupos hidroxi-alquilo de cadena ramificada o recta, como se utilizan en la presente, incluyen los grupos metilo, etilo, propilo, isopropilo, isobutilo y butilo normal sustituidos con uno o más grupos hidroxilo.

El término "isocianato", como se utiliza en la presente, se refiere a un grupo –N=C=O.

El término "isotiocianato", como se utiliza en la presente, se refiere a un grupo –N=C=S.

El término "mercaptilo", como se utiliza en la presente, se refiere a un grupo (alquil)S-.

El término "opcionalmente sustituido", como se utiliza en la presente, significa que el grupo referenciado puede o no estar sustituido con uno o más grupos adicionales individualmente e independientemente seleccionados a partir de alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, hetero-cicloalquilo, hidroxilo, alcoxilo, mercaptilo, ciano, halógeno, carbonilo, tiocarbonilo, isocianato, tiocianato, isotiocianato, nitro, perhalo-alquilo, perfluoro-alquilo, y amino, incluyendo los grupos amino mono- y di-sustituidos, y los derivados protegidos de los mismos. Los ejemplos no limitantes de los sustituyentes opcionales incluyen halógeno, –CN, =O, –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, -$S(O)_2$R, -NHR, -$N(R)_2$, -NHC(O)R, –NRC(O)R, -NHC(O)OR, -NRC(O)OR, $S(O)_2$NHR, –$S(O)_2N(R)_2$,

$-NHS(O)_2$, $-NRS(O)_2$, $-NHS(O)_2R$, $-NRS(O)_2R$, alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, arilo, heteroarilo, cicloalquilo, hetero-cicloalquilo, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno, en donde cada R se selecciona independientemente a partir de H, halógeno, alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, arilo, heteroarilo, cicloalquilo, hetero-cicloalquilo, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, y alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno. La colocación y el número de estos grupos sustituyentes se hacen de acuerdo con las limitaciones de valencia bien entendidas de cada grupo, por ejemplo =O es un sustituyente adecuado para un grupo alquilo pero no para un grupo arilo.

El término "solvato", como se utiliza en la presente, se refiere a un complejo de estequiometría variable formado por un soluto (a manera de ejemplo, un compuesto de la fórmula (I), o una sal del mismo, como se describe en la presente), y un solvente. Los ejemplos no limitantes de un solvente son agua, acetona, metanol, etanol, y ácido acético.

El término "aceptable" con respecto a una formulación, composición o ingrediente, como se utiliza en la presente, significa que no tiene un efecto perjudicial persistente sobre la salud general del sujeto que se esté tratando.

El término "administración" o "administrar" al sujeto el compuesto, significa proporcionar un compuesto de la invención y

pro-fármacos del mismo a un sujeto que necesite tratamiento.

El término "enfermedad ósea", como se utiliza en la presente, se refiere a una enfermedad o condición de los huesos, incluyendo, pero no limitándose a, remodelación, pérdida o ganancia ósea inapropiada, osteopenia, osteomalacia, osteofibrosis, y enfermedad de Paget.

El término "enfermedad cardiovascular", como se utiliza en la presente, se refiere a enfermedades que afectan al corazón o a los vasos sanguíneos, o a ambos, incluyendo, pero no limitándose a: arritmia; ateroesclerosis y sus secuelas; angina; isquemia de miocardio; infarto de miocardio; aneurisma cardíaco o vascular; vasculitis, embolia; arteriopatía obstructiva periférica de una extremidad, un órgano, o un tejido; lesión por reperfusión en seguida de isquemia del cerebro, corazón, u otro órgano o tejido; choque endotóxico, quirúrgico, o traumático; hipertensión, enfermedad cardíaca valvular, insuficiencia cardíaca, presión sanguínea anormal; choque; vasoconstricción (incluyendo aquélla asociada con migrañas); anormalidad vascular, inflamación, insuficiencia limitada a un solo órgano o tejido.

El término "cáncer,", como se utiliza en la presente, se refiere a un crecimiento anormal de células que tienden a proliferar de una manera incontrolada, y, en algunos casos, a metastatatizarse (extenderse). Los tipos de cáncer incluyen, pero no se limitan a, tumores sólidos (tales como aquéllos de la vejiga, intestino, cerebro, mama, endometrio, corazón, riñón, pulmón, tejido linfático (linfoma),

ovario, páncreas, u otro órgano endocrino (tiroides), próstata, piel (melanoma)), o tumores hematológicos (tales como las leucemias).

El término "vehículo", como se utiliza en la presente, se refiere a compuestos químicos o agentes que facilitan la incorporación de un compuesto descrito en la presente en las células o tejidos.

Los términos "co-administración" o "administración combinada", o similares, como se utilizan en la presente, pretenden abarcar la administración de los agentes terapéuticos seleccionados a un solo paciente, y se pretende que incluyan los regímenes de tratamiento en donde los agentes no necesariamente se administren por la misma vía de administración o al mismo tiempo.

El término "trastorno dermatológico", como se utiliza en la presente, se refiere a un trastorno de la piel. Estos trastornos dermatológicos incluyen, pero no se limitan a, trastornos proliferativos o inflamatorios de la piel, tales como dermatitis atópica, trastornos bullosos, colagenosis, dermatitis por contacto, eczema, Enfermedad de Kawasaki, rosácea, Síndrome de Sjogren-Larsso, y urticaria.

El término "diluyente", como se utiliza en la presente, se refiere a los compuestos químicos que se utilizan para diluir un compuesto descrito en la presente antes de su suministro. También se pueden utilizar diluyentes para estabilizar los compuestos descritos en la presente.

Los términos "cantidad efectiva" o "cantidad terapéuticamente efectiva", como se utilizan en la presente, se refieren a una cantidad

suficiente de un compuesto descrito en la presente que, al administrarse, aliviarán hasta algún grado uno o más de los síntomas de la enfermedad o condición que se esté tratando. El resultado puede ser la reducción y/o el alivio de los signos, síntomas, o causas de una enfermedad, o cualquier otra alteración deseada de un sistema biológico. Por ejemplo, una "cantidad efectiva" para usos terapéuticos es la cantidad de la composición que comprende un compuesto como se da a conocer en la presente, requerida para proporcionar disminución clínicamente significativa en los síntomas de la enfermedad. Una cantidad "efectiva" apropiada en cualquier caso individual se puede determinar empleando técnicas tales como un estudio de escala de dosis.

Los términos "mejorar" o "mejora", como se utilizan en la presente, significan aumentar o prolongar ya sea la potencia o bien la duración de un efecto deseado. Por consiguiente, con respecto a mejorar el efecto de los agentes terapéuticos, el término "mejorar" se refiere a la capacidad para aumentar o prolongar ya sea la potencia o bien la duración del efecto de otros agentes terapéuticos sobre un sistema. Una "cantidad mejoradora efectiva", como se utiliza en la presente, se refiere a una cantidad adecuada para mejorar el efecto de otro agente terapéutico en un sistema deseado.

Los términos "fibrosis" o " trastorno fibrosante", como se utiliza en la presente, se refiere a las condiciones que siguen a una inflamación aguda o crónica, y están asociadas con la acumulación anormal de células y/o colágeno, e incluyen, pero no se limitan a,

fibrosis de los órganos o tejidos individuales, tales como el corazón, riñón, articulaciones, pulmón, o piel, e incluyen los trastornos tales como fibrosis pulmonar idiopática y alveolitis fibrosante criptogénica.

El término "iatrogénico", como se utiliza en la presente, significa una condición, trastorno, o enfermedad creada o empeorada por la terapia médica o quirúrgica.

El término "trastornos inflamatorios", como se utiliza en la presente, se refiere a las enfermedades o condiciones que se caracterizan por uno o más de los signos de dolor (dolor, a partir de la generación de sustancias nocivas y el estímulo de los nervios), calor (calor, a partir de la vasodilatación), enrojecimiento (rubor, a partir de la vasodilatación y del mayor flujo sanguíneo), hinchamiento (tumor, a partir de un influjo excesivo o de un exflujo restringido de fluido), y pérdida de función (*functio laesa*, que puede ser parcial o completa, temporal o permanente). La inflamación toma muchas formas, e incluye, pero no se limita a, inflamación que es una o más de las siguientes: aguda, adhesiva, atrófica, catarral, crónica, cirrótica, difusa, diseminada, exudativa, fibrinosa, fibrosante, focal, granulomatosa, hiperplásica, hipertrófica, intersticial, metastásica, necrótica, obliterativa, parenquimatosa, plásica, productiva, proliferante, pseudo-membranosa, purulenta, esclerosante, seroplásica, serosa, simple, específica, sub-aguda, supurativa, tóxica, traumática, y/o ulcerativa. Los trastornos inflamatorios incluyen además, sin limitarse a aquéllos que afectan a los vasos sanguíneos (poliarteritis, arteritis temporal); a las articulaciones

(artritis: cristalina, osteoartritis, soriática, reactiva, reumatoide, de Reiter); al tracto gastrointestinal (Enfermedad); a la piel (dermatitis); o a múltiples órganos y tejidos (lupus eritematoso sistémico).

El término "Panel de Cinasa", como se utiliza en la presente, se refiere a una lista de cinasas que incluye, pero no se limita a, Abl(humana), Abl(T315I), JAK2, JAK3, ALK, JNK1α1, ALK4, KDR, Aurora-A, Lck, Blk, MAPK1, Bmx, MAPKAP-K2, BRK, MEK1, CaMKII(rata), Met, CDK1/ciclinaB, p70S6K, CHK2, PAK2, CK1, PDGFRα, CK2, PDK1, c-Kit, Pim-2, C-Raf, PKA(h), CSK, PKBα, Src, PKCα, DYRK2, Plk3, EGFR, ROCK-I, Fes, Ron, FGFR-3, Ros, Flt3, SAPK2α, Fms, SGK, Fyn, SIK, GSK3ß, Syk, IGFR, Tie-2, IKKß, IR, WNK3, IRAK4, ZAP-70, ITK, AMPK(rata), LIMK1, Rsk2, Axl, LKB1, SAPK2ß, BrSK2, Lyn (humana), SAPK3, BTK, MAPKAP-K3, SAPK4, CaMKIV, MARK1, Snk, CDK2/ciclinaA, MINK, SRPK1, CDK3/ciclina, MKK4(ratón), TAK1, CDK5/p25, MKK6(humana), TBK1, CDK6/ ciclinaD3, MLCK, TrkA, TrkB, TrkC, CDK7/ciclinaH/MAT1, MRCKß, TSSK1, CHK1, MSK1, Yes, CK1d, MST2, ZIPK, c-Kit (D816V), MuSK, DAPK2, NEK2, DDR2, NEK6, DMPK, PAK4, DRAK1, PAR-1Bα, EphA1, PDGFRß, EphA2, Pim-1, EphA5, PKBß, EphB2, PKCßI, EphB4, PKCδ, FGFR1, PKCη, FGFR2, PKCθ, FGFR4, PKD2, Fgr, PKG1ß, Flt1, PRK2, Hck, PYK2, HIPK2, Ret, IKKα, RIPK2, IRR, ROCK-II(humana), JNK2α2, Rse, JNK3, Rsk1(humana), PI3 Kγ, PI3 Kδ, y PI3-Kß.

El término "modular", como se utiliza en la presente, significa interactuar con un objetivo ya sea directa o indirectamente como

para alterar la actividad del objetivo, incluyendo, a manera de ejemplo solamente, para mejorar la actividad del objetivo, para inhibir la actividad del objetivo, para limitar la actividad del objetivo, o para extender la actividad del objetivo.

El término "modulador", como se utiliza en la presente, se refiere a una molécula que interactúa con un objetivo ya sea directa o indirectamente. Las interacciones incluyen, pero no se limitan a, las interacciones de un agonista y un antagonista.

Los términos "enfermedad neurodegenerativa" o "trastorno del sistema nervioso", como se utiliza en la presente, se refiere a las condiciones que alteran la estructura o la función del cerebro, la médula espinal, o el sistema nervioso periférico, incluyendo, pero no limitándose a, enfermedad de Alzheimer, edema cerebral, isquemia cerebral, esclerosis múltiple, neuropatías, Enfermedad de Parkinson, aquéllas encontradas después de embotamiento o trauma quirúrgico (incluyendo disfunción cognitiva post-quirúrgica, y lesión de la médula espinal o del tallo cerebral), así como los aspectos neurológicos de los trastornos, tales como enfermedad degenerativa de discos, y ciática. El acrónimo "CNS" se refiere a trastornos del sistema nervioso central (cerebro y médula espinal).

Los términos "enfermedad ocular" o "enfermedad oftálmica", como se utiliza en la presente, se refieren a enfermedades que afectan al ojo o a los ojos, y potencialmente los tejidos circundantes también. Las enfermedades oculares u oftálmicas incluyen, pero no se limitan a, conjuntivitis, retinitis, escleritis, uveítis, conjuntivitis

alérgica, conjuntivitis primaveral, conjuntivitis papilar.

El término "farmacéuticamente aceptable", como se utiliza en la presente, se refiere a un material, tal como un vehículo o diluyente, que no abroga la actividad biológica o las propiedades de los compuestos descritos en la presente. Estos materiales se administran a un individuo sin causar efectos biológicos indeseables, o sin interactuar de una manera perjudicial con cualquiera de los componentes de la composición en donde están contenidos.

El término "sal farmacéuticamente aceptable", como se utiliza en la presente, se refiere a una formulación de un compuesto que no provoca una irritación significativa a un organismo al que se administra, y que no abroga la actividad biológica y las propiedades de los compuestos descritos en la presente.

El término "combinación farmacéutica", como se utiliza en la presente, significa un producto que resulta de la mezcla o combinación de más de un ingrediente activo, e incluye tanto las combinaciones fijas como no fijas de los ingredientes activos. El término "combinación fija" significa que los ingredientes activos, por ejemplo, un compuesto de la fórmula I, y un co-agente, se administran ambos a un paciente de una manera simultánea en la forma de una sola entidad o dosificación. El término "combinación no fija" significa que los ingredientes activos, por ejemplo, un compuesto de la fórmula I, y un co-agente, se administran ambos a un paciente como entidades separadas, ya sea de una manera simultánea, concurrente, o en secuencia, sin límites de tiempo

específicos, en donde esta administración proporcione niveles terapéuticamente efectivos de los dos compuestos en el cuerpo del paciente. Esto último también se aplica a la terapia de cóctel, por ejemplo, la administración de tres o más ingrediente activos.

El término "composición farmacéutica", como se utiliza en la presente, se refiere a una mezcla de un compuesto descrito en la presente con otros componentes químicos, tales como vehículos, estabilizantes, diluyentes, agentes dispersantes, agentes de suspensión, agentes espesantes, y/o excipientes.

El término "pro-fármaco", como se utiliza en la presente, se refiere a un agente que se convierte en el fármaco progenitor *in vivo*. Los pro-fármacos son con frecuencia útiles debido a que, en algunas situaciones, pueden ser más fáciles de administrar que el fármaco progenitor. Los pro-fármacos están biodisponibles mediante administración oral, mientras que el progenitor no lo está. Los pro-fármacos mejoran la solubilidad en las composiciones farmacéuticas sobre el fármaco progenitor. Un ejemplo no limitante de un pro-fármaco de los compuestos descritos en la presente, es un compuesto descrito en la presente administrado como un éster, el cual entonces se hidroliza metabólicamente hasta un ácido carboxílico, la entidad activa, una vez que está dentro de la célula. Un ejemplo adicional de un pro-fármaco es un péptido corto enlazado a un grupo ácido, en donde el péptido se metaboliza para revelar la fracción activa.

El término "enfermedad respiratoria", como se utiliza en la

185

presente, se refiere a las enfermedades que afectan a los órganos que están involucrados en la respiración, tales como la nariz, garganta, laringe, tráquea, bronquios, y pulmones. Las enfermedades respiratorias incluyen, pero no se limitan a, asma, síndrome de insuficiencia respiratoria de adultos, y asma alérgico (extrínseco), asma no alérgico (intrínseco), asma agudo grave, asma crónico, asma clínico, asma nocturno, asma inducido por alergeno, asma sensible a la aspirina, asma inducido por ejercicio, hiperventilación isocápnica, asma de establecimiento en la infancia, asma resistente a esteroides, asma de temporada, rinitis alérgica de temporada, rinitis alérgica perenne, enfermedad pulmonar obstructiva crónica, incluyendo bronquitis crónica o enfisema, hipertensión pulmonar, fibrosis pulmonar intersticial, y/o inflamación de las vías respiratorias y fibrosis quística, e hipoxia.

El término "sujeto" o "paciente", como se utiliza en la presente, abarca mamíferos y no mamíferos. Los ejemplos de los mamíferos incluyen, pero no se limitan a, seres humanos, chimpancés, monos, ganado, caballos, ovejas, cabras, cerdos; conejos, perros, gatos, ratas, ratones, cobayos, y similares. Los ejemplos de los no mamíferos incluyen, pero no se limitan a, aves, peces, y similares.

El término "cantidad terapéuticamente efectiva", como se utiliza en la presente, se refiere a cualquier cantidad de un compuesto que, comparándose con un sujeto correspondiente que no haya recibido dicha cantidad, da como resultado un mejor tratamiento, el sanado, la prevención, o la mejoría de una enfermedad, trastorno, o efecto

secundario, o una disminución en el índice de avance de una enfermedad o trastorno. El término también incluye, dentro de su alcance, las cantidades efectivas para mejorar la función fisiológica normal.

Los términos "tratar", "tratando" o "tratamiento,", como se utilizan en la presente, se refieren a los métodos para aliviar, abatir, o mejorar los síntomas de una enfermedad o condición, para prevenir síntomas adicionales, para mejorar o prevenir las causas metabólicas subyacentes de los síntomas, para inhibir la enfermedad o condición, para detener el desarrollo de la enfermedad o condición, para aliviar la enfermedad o condición, para provocar la regresión de la enfermedad o condición, para aliviar una condición causada por la enfermedad o condición, o para detener los síntomas de la enfermedad o condición, ya sea profilácticamente y/o terapéuticamente.

Los términos "uso" o "usado", como se utilizan en la presente, pretenden incluir un compuesto de la fórmula (I) proporcionado en la presente, para utilizarse en el tratamiento profiláctico y/o terapéutico de una o más enfermedades proporcionadas en la presente, un método de uso o un método de tratamiento, el cual comprende administrar un compuesto de la fórmula (I) a una persona que necesite dicho tratamiento, en una cantidad efectiva para el tratamiento profiláctico y/o terapéutico de una o más enfermedades proporcionadas en la presente, la preparación o un método de preparación de una formulación farmacéutica/preparación para

utilizarse en el tratamiento profiláctico y terapéutico de una o más enfermedades proporcionadas en la presente, en especial que involucra mezclar un compuesto de la fórmula (I) (como ingrediente terapéuticamente activo) con cuando menos un material portador farmacéuticamente aceptable, incluyendo dejarlo listo para utilizarse en dicho tratamiento (por ejemplo, agregar un inserto de instrucciones (por ejemplo, folleto del paquete, o similar), formulación, preparación apropiada, adaptación para usos específicos, adecuación a la medida, y similares), y el uso de un compuesto de la fórmula (I) para esta preparación, y/o todos los demás usos profilácticos o terapéuticos mencionados en la presente.

Otros objetos, características, y ventajas de los métodos y composiciones descritos en la presente, llegarán a ser evidentes a partir de la siguiente descripción detallada. Se debe entender, sin embargo, que la descripción detallada y los ejemplos específicos, aunque indican modalidades específicas, se dan solamente a manera de ilustración.

Compuestos

En la presente se proporcionan compuestos, sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, los cuales son moduladores de la actividad de cinasa. En la presente se proporcionan compuestos, sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, los cuales son moduladores de las cinasas de proteína. También en la presente se proporcionan compuestos,

sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, composiciones farmacéuticas, combinaciones farmacéuticas y métodos para el tratamiento y/o la prevención de las enfermedades o condiciones/trastornos relacionados con la cinasa de proteína, incluyendo las enfermedades o condiciones/trastornos asociados con una actividad anormal o mal regulada de la cinasa de proteína. En ciertas modalidades, los compuestos, sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, proporcionados en la presente, son moduladores de las cinasas de proteína Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK. En ciertas modalidades, los compuestos, sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, proporcionados en la presente, son inhibidores de las cinasas de proteína Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK. En ciertas modalidades, los compuestos, sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, proporcionados en la presente, son inhibidores de las cinasas de proteína TrkA, TrkB, TrkC, IGF-1R, y/o ALK. En otras modalidades, los compuestos, sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, proporcionados en la presente, se utilizan para tratar y/o prevenir enfermedades y condiciones relacionadas con, o mediadas por, Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2,

JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGR-1R, ALK4, ALK5, ALK, o una combinación de las mismas. En otras modalidades, los compuestos, sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, proporcionados en la presente, se utilizan para tratar y/o prevenir enfermedades y condiciones relacionadas con, o mediadas por, las cinasas de proteína TrkA, TrkB, TrkC, IGR-1R, ALK, o una combinación de las mismas.

Además, en la presente se proporcionan compuestos, sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, y composiciones farmacéuticas que contienen estas sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, para el tratamiento y/o la prevención de enfermedades y/o trastornos en donde una actividad aberrante, anormal o mal regulada de la cinasa de proteína Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGR-1R, ALK4, ALK5, o ALK contribuya a la patología y/o sintomatología de estas enfermedades y/o trastornos. También en la presente se proporcionan compuestos, sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, y composiciones farmacéuticas que contienen estas sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, para el tratamiento y/o la prevención de enfermedades y/o trastornos en donde una actividad aberrante, anormal o mal regulada de la cinasa de proteína

TrkA, TrkB, TrkC, IGR-1R, o ALK contribuya a la patología y/o sintomatología de estas enfermedades y/o trastornos.

En ciertas modalidades, estas enfermedades y/o trastornos incluyen, pero no se limitan a, cáncer, enfermedades proliferativas, dolor, enfermedades y/o trastornos dermatológicos, enfermedades y/o trastornos metabólicos, enfermedades y/o trastornos musculares, enfermedades y/o trastornos neurodegenerativos, enfermedades y/o trastornos neurológicos, enfermedades y/o trastornos de inmunodeficiencia, enfermedades y/o trastornos inmunológicamente mediados, enfermedades autoinmunes, enfermedades auto-inmunológicamente mediadas, enfermedades y/o trastornos óseos, enfermedades inflamatorias, fibrosis, enfermedades y/o trastornos oftálmicos/oculares, enfermedades infecciosas, enfermedades virales, reparación de heridas, enfermedades y/o trastornos respiratorios, enfermedades y/o trastornos pulmonares, enfermedad renal, enfermedad del riñón, enfermedad hepática, enfermedades y/o trastornos cardiovasculares, enfermedades y/o trastornos vasculares, enfermedad cardíaca, muerte celular, e hiperplasia.

Las enfermedades de cáncer y proliferativas incluyen, pero no se limitan a, trastornos hematopoiéticos, malignidades hematopoiéticas, malignidades no hematopoiéticas, tumores benignos o malignos, tumores de cuello y cabeza, cáncer de cerebro, cáncer de riñón, cáncer de hígado, cáncer de glándula suprarrenal, cáncer neuronal, neuroblastoma, cáncer de vejiga, cáncer de mama, carcinoma secretor de mama, cáncer de estómago, tumores

1858

gástricos, cáncer de ovario, cáncer uterino, cáncer de colon, cáncer rectal, adenoma colo-rectal, cáncer de próstata, cáncer renal, cáncer de cerebro, cáncer endometrial, cáncer pancreático, cáncer de pulmón, cáncer pulmonar no microcelular, carcinoma quístico adenoideo humano, cáncer vaginal, cáncer de tiroides, carcinoma papilar de tiroides, sarcoma, fibrosarcoma congénito, sarcoma osteolítico, osteosarcoma, fibrosarcoma, mieloma, metástasis tumoral ósea, nefroma mesoblástico congénito, glioblastomas, melanoma, mieloma múltiple, cáncer gastrointestinal, tumores estromales gastrointestinales (GIST), mastocitosis, neuroblastoma, cánceres fibróticos, crecimiento de metástasis tumoral, hiperproliferación epidérmica, soriasis, metástasis, hiperplasia de próstata, neoplasia, neoplasia de carácter epitelial, linfomas, linfoma grande y difuso de células-B, linfoma de células-B, carcinoma mamario, tumor de Wilm, síndrome de Cowden, enfermedad de Lhermitte-Dudos, y síndrome de Bannayan-Zonana.

Los trastornos hematopoiéticos incluyen, pero no se limitan a, trastornos mieloproliferativos, trombocitemia, trombocitosis esencial (ET), metaplasia mieloide angiogénica, mielofibrosis (MF), mielofibrosis con metaplasia mieloide (MMM), mielofibrosis idiopática crónica (IMF), policitemia vera (PV), las citopenias, y síndromes mielodisplásicos pre-malignos.

Las malignidades hematológicas incluyen, pero no se limitan a, leucemias, leucemias mieloides, leucemia de células pilosas, linfomas (linfoma no de Hodgkin), enfermedad de Hodgkin (también

denominada como linfoma de Hodgkin), y mieloma, incluyendo, pero no limitándose a, leucemia linfocítica aguda (ALL), leucemia mieloide aguda (AML), leucemia pro-mielocítica aguda (APL), leucemia linfocítica crónica (CLL), leucemia mieloide crónica (CML), leucemia neutrofílica crónica (CNL), leucemia no diferenciada aguda (AUL), linfoma macrocelular anaplásico (ALCL), leucemia pro-linfocítica (PML), leucemia mielomonocítica juvenil (JMML), leucemia linfocítica aguda de células-T de adultos, leucemia mieloide aguda con mielodisplasia de tri-linaje (AML/TMDS), leucemia de linaje mixto (MLL), síndromes mielodisplásicos (MDSs), trastornos mielo-proliferativos (MPD), mieloma múltiple, (MM), sarcoma mieloide, y leucemia pro-mielocítica aguda (APL).

Los trastornos de dolor incluyen, pero no se limitan a, dolor relacionado con cáncer, dolor esquelético causado por metástasis tumoral, osteoartritis, dolor visceral, dolor inflamatorio, y dolor neurogénico.

Las enfermedades y/o los trastornos dermatológicos incluyen, pero no se limitan a, condiciones inflamatorias o alérgicas de la piel, dermatitis, eczema, soriasis, dermatitis atópica, dermatitis seborreica (caspa, costra láctea), irritación por el pañal, dermatitis por contacto inducida por urushiol, dermatitis por contacto, eritrodermia, liquen simple crónico, prurigo nodular, comezón, prurito anal, dermatitis numular, dishidrosis, pitiriasis alba, alopecia areata, eritema multiforme, dermatitis herpetiforme, esclerodermia, vitiligo, angiitis por hipersensibilidad, urticaria, penfigoide bulloso, lupus

eritematoso, pénfigo, epidermólisis bullosa adquirida, adhesión peritoneal y subdérmica, y fotoenvejecimiento de la piel.

Las enfermedades y/o los trastornos metabólicos y trastornos en el comer incluyen, pero no se limitan a, obesidad, diabetes, y anorexia.

Las enfermedades y/o los trastornos musculares incluyen, pero no se limitan a, atrofias musculares (por ejemplo, desuso), distrofias musculares (por ejemplo, distrofia muscular de Duchenne, distrofia muscular de Becker, distrofia muscular de la cintura escapulohumeral o pélvica), sarcopenia, caquexia, consunción, y distrofia facioescapulohumeral.

Las enfermedades y/o los trastornos neurológicos y los trastornos neurodegenerativos incluyen, pero no se limitan a, función neurológica deteriorada y enfermedad de Alzheimer.

Las enfermedades y/o los trastornos de inmunodeficiencia y las enfermedades y/o los trastornos inmunológicamente mediados incluyen, pero no se limitan a, condiciones inmunológicas patológicas que involucran activación de las células-T, anafilaxis, alergia, y soriasis. Los trastornos de alergia incluyen, pero no se limitan a, enfermedades respiratorias y trastornos dermatológicos.

Las enfermedades y/o los trastornos autoinmunes y las enfermedades y/o los trastornos auto-inmunológicamente mediados incluyen, pero no se limitan a, artritis destructiva, artritis reumatoide, lupus eritematoso sistémico, síndrome de Sjogren, esclerosis múltiple, dermatomiositis, esclerosis sistémica progresiva,

enfermedades que afecten a la nariz, incluyendo rinitis alérgica, y enfermedad inflamatoria en donde estén implicadas reacciones autoinmunes o que tenga un componente o etiología autoinmune, incluyendo trastornos hematológicos autoinmunes (por ejemplo, anemia hemolítica, anemia aplásica, anemia de glóbulos rojos puros, y trombocitopenia idiopática), cirrosis biliar primaria (PBC), lupus, lupus eritematoso sistémico, policondritis, esclerodoma, granulomatosis de Wegener, dermatomiositis, hepatitis activa crónica, miastenia grave, síndrome de Steven-Johnson, prurito idiopático, enfermedad inflamatoria autoinmune del intestino (por ejemplo, colitis ulcerativa y enfermedad de Crohn), oftalmopatía endocrina, enfermedad de Graves, sarcoidosis, alveolitis, neumonitis de hipersensibilidad crónica, esclerosis múltiple, cirrosis biliar primaria, uveítis (anterior y posterior), queratoconjuntivitis sicca y queratoconjuntivitis vernal, fibrosis pulmonar intersticial, artritis soriática, y glomerulonefritis (con y sin síndrome nefrótico, por ejemplo, incluyendo síndrome nefrótico idiopático o nefropatía de cambio mínimo).

Las enfermedades y/o los trastornos óseos incluyen, pero no se limitan a, osteoporosis, osteítis deformante, enfermedad de Paget, osteoartritis, falla de prótesis, osteopenia, y fracturas y otros trastornos en donde una baja densidad mineral ósea sea un signo de la enfermedad.

Las enfermedades y/o los trastornos inflamatorios incluyen, pero no se limitan a, uveítis, ateroesclerosis, aterogénesis,

glomerulonefritis, enfermedad de Kawasaki, respuestas inflamatorias, polimiositis, artritis, inflamación neurológica, inflamación por artritis crónica, y osteoartritis.

Las enfermedades y/o los trastornos de fibrosis incluyen, pero no se limitan a, acumulación de matriz extracelular y fibrosis, esclerodermia, fibroesclerosis, fibrosis inducida por radiación, fibrosis del riñón, fibrosis pulmonar y fibrosis hepática, hemocromatosis, cirrosis biliar primaria, restenosis, fibrosis retroperitoneal, fibrosis mesentérica, endometriosis, y queloides.

Las enfermedades y/o los trastornos oftálmicos/oculares incluyen, pero no se limitan a, vítreo-retinopatía proliferativa, escarificación ocular, escarificación de córnea, trastornos oculares, heridas de córnea, conjuntivitis, queratoconjuntivitis sicca, y conjuntivitis vernal.

Las infecciones y enfermedades y/o trastornos virales incluyen, pero no se limitan a, infección por VIH-1, por ejemplo, virus de hepatitis B (HBV), virus de hepatitis C (HCV), hepatitis inducida por alcohol.

La reparación de heridas incluye, pero no se limita a, formación excesiva o hipertrófica de escara o queloide en la dermis que se presente durante sanado de heridas resultantes de trauma, o de heridas quirúrgicas, úlceras (incluyendo úlceras diabéticas, úlceras crónicas, úlceras gástricas, y úlceras duodenales).

Las enfermedades y/o los trastornos respiratorios y los trastornos pulmonares incluyen, pero no se limitan a, asma, asma

bronquial, asma alérgico, asma intrínseco (no alérgico), asma extrínseco (alérgico), asma inducido por ejercicio, asma inducido por fármacos (incluyendo inducido por aspirina y por fármacos anti-inflamatorios no esteroideos (NSAID)), y asma inducido por polvo, enfermedad pulmonar obstructiva crónica (COPD); enfermedad obstructiva crónica de las vías respiratorias (COAD), enfermedad obstructiva crónica del pulmón (COLD), bronquitis, bronquitis crónica, bronquitis aguda, disnea, bronquitis araquídica, bronquitis catarral, bronquitis cruposa, bronquitis ftinoide, rinitis, rinitis aguda, rinitis crónica, rinitis medicamentosa, rinitis vasomotora, rinitis alérgica perenne y de temporada, rinitis nerviosa (fiebre de heno), enfermedades inflamatorias u obstructivas de las vías respiratorias, hipertensión pulmonar, lesión pulmonar aguda, síndrome de insuficiencia respiratoria de adultos/aguda (ARDS), fibrosis pulmonar, fibrosis pulmonar idiopática, enfermedad pulmonar obstructiva crónica, enfermedad pulmonar debida a agentes infecciosos o tóxicos, enfisema, neumoconiosis, aluminosis, antracosis, asbestosis, calicosis, ptilosis, siderosis, silicosis, tabacosis, bisinosis, lesión pulmonar aguda (ALI), hipereosinofilia, síndrome de Löffler, neumonía eosinofílica, infestación parasitaria (en particular de metazoarios) (incluyendo eosinofilia tropical), aspergilosis broncopulmonar, poliarteritis nodosa (incluyendo síndrome de Churg-Strauss), granuloma eosinofílico, trastornos relacionados con los eosinófilos que afecten a las vías respiratorias, ocasionados por reacción a fármacos, hipertensión pulmonar,

hipertensión pulmonar primaria (PPH), hipertensión pulmonar secundaria (SPH), hipertensión pulmonar primaria familiar, hipertensión pulmonar primaria esporádica, hipertensión pulmonar pre-capilar, hipertensión arterial pulmonar (PAH), hipertensión de arteria pulmonar, hipertensión pulmonar idiopática, arteriopatía pulmonar trombótica (TPA), arteriopatía pulmonar plexogénica, arteriopatía pulmonar funcional clases I a IV, e hipertensión pulmonar asociada con, relacionada con, o secundaria a, disfunción de ventrículo izquierdo, enfermedad de válvula mitral, pericarditis constrictiva, estenosis aórtica, cardiomiopatía, fibrosis mediastinal, drenaje venoso pulmonar anómalo, enfermedad oclusiva venosa pulmonar, enfermedad vascular de colágeno, enfermedad cardíaca congénita, infección por virus VIH, fármacos y toxinas, tales como fenfluraminas, hipoxemia, hipertensión venosa pulmonar, enfermedad pulmonar obstructiva crónica, enfermedad intersticial pulmonar, respiración trastornada en el sueño, trastorno de hipoventilación alveolar, exposición crónica a alta altitud, enfermedad pulmonar neonatal, displasia capilar alveolar, enfermedad drepanocítica, otro trastorno de la coagulación, tromboémbolos crónicos, enfermedad del tejido conectivo, lupus, esquistosomiasis, sarcoidosis, o hemangiomatosis capilar pulmonar.

Las enfermedades y/o los trastornos renales incluyen, pero no se limitan a, glomerulonefritis, fibrosis intersticial renal, fibrosis renal, enfermedad renal crónica y enfermedad renal aguda. Las enfermedades y/o los trastornos del riñón incluyen, pero no se

limitan a, nefropatía diabética, nefritis por lupus, nefropatía inducida por hipertensión, nefropatía asociada con VIH y necropatía de trasplante. Las enfermedades y/o los trastornos del hígado incluyen, pero no se limitan a, disfunción hepática atribuible a infecciones, hepatitis inducida por alcohol, trastornos del árbol biliar, e isquemia hepática.

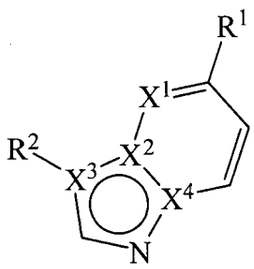
Las enfermedades y/o los trastornos cardiovasculares, vasculares, o cardíacos incluyen, pero no se limitan a, insuficiencia cardíaca congestiva, fibrosis cardíaca posterior a infarto, insuficiencia cardíaca congestiva, reperfusión/isquemia en embolia, ataques al corazón, e hipoxia de órganos, isquemia, cardiomiopatía dilatada, miocarditis, infarto de miocardio, estenosis vascular, restenosis, ateroesclerosis, disfunción eréctil masculina, síndrome de Raynaud, trombosis, y acumulación de plaquetas inducida por trombina.

En otras modalidades, los compuestos de la fórmula (I) proporcionados en la presente son agentes inmunosupresores, y se utilizan para tratar rechazo de trasplante de órgano, rechazo crónico de trasplante, lupus, esclerosis múltiple, artritis reumatoide, soriasis, dermatitis, enfermedad de Crohn, diabetes tipo-1 y complicaciones de diabetes tipo-1.

En ciertas modalidades, los compuestos, sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, y las composiciones farmacéuticas y combinaciones farmacéuticas proporcionadas en la presente, son

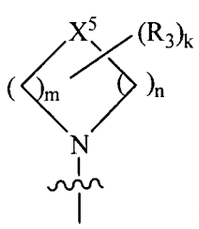
inhibidores de la actividad de cinasa de proteína Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGR-1R, ALK4, ALK5, y/o ALK.

Los compuestos anteriormente mencionados, y las sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, son compuestos que tienen estructuras de acuerdo con la fórmula (I).



Fórmula (I)

en donde:

R^1 es  ; en donde:

X^1, X^2 X^3 y X^4 son cada uno independientemente CR^9, C, o N, con la condición de que cuando menos uno de X^1, X^2 X^3 y X^4 es N, y cuando mucho solamente dos de X^1, X^2 X^3 y X^4 son N;

X^5 es $C(R^3)_2$, O, S, $S(O)_2$, S(O), o N;

m es 1, 2, 3 ó 4;

n es 0, 1, 2 ó 3;

k es 0, 1, 2, 3, 4, 5 ó 6;

cada R^3 se selecciona independientemente a partir de halógeno, nitro, $-N(R^4)_2$, $-OR^9$, -CN, =O, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-C(O)OR^9$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, $-OC(O)R^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, alquilo de 1 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono y heteroarilo de 2 a 13 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono y heteroarilo de 2 a 13 átomos de carbono de R^3 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, amino, nitro, hidroxilo, ciano, $-OR^9$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-C(O)OR^9$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, $-OC(O)R^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, alquilo de 1 a 8 átomos de carbono, amino-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de

carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno, cicloalquilo de 3 a 8 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, arilo de 6 a 14 átomos de carbono, y heteroarilo de 2 a 13 átomos de carbono;

de una manera alternativa, cada R^3 es independientemente un alquilo de 1 a 8 átomos de carbono, en donde cuando menos dos R^3 forman juntos un cicloalquilo de 3 a 8 átomos de carbono fusionado con un heterociclo, y en donde cada alquilo de 1 a 8 átomos de carbono de R^3 está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, amino, nitro, hidroxilo, ciano, $-OR^9$, alquilo de 1 a 8 átomos de carbono, amino-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno, cicloalquilo de 3 a 8 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, arilo de 6 a 14 átomos de carbono, y heteroarilo de 2 a 13 átomos de carbono;

R^2 es arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono o hetero-cicloalquilo de 2 a 14 átomos de carbono, en donde el arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono o hetero-cicloalquilo de 2 a 14 átomos de carbono de R^2 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de

halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-OC(O)R^9$, alcoxilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno y alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno;

cada R^4 se selecciona independientemente a partir de H, alquilo de 1 a 8 átomos de carbono, $-L^1R^5$, $-L^1R^6$, $-L^1R^8$, heteroarilo de 2 a 13 átomos de carbono, arilo de 6 a 14 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, y cicloalquilo de 3 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, y cicloalquilo de 3 a 8 átomos de carbono están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, deuterio, $-CD_3$, $-S(O)_2R^9$, -CN, alquilo de 1 a 8 átomos de carbono, $-OR^9$, $-N(R^9)_2$ y $-(CH_2)_pOR^9$;

L^1 es un enlace, alquileno de 1 a 8 átomos de carbono, alquenileno de 2 a 8 átomos de carbono, $-O(CH_2)_p-$, -C(O)-, $-N(R^9)$, $-CH_2)_pC(O)-$, $-C(O)(CH_2)_pO(CH_2)_p-$, o -C(O)O-;

Y^1 es arileno de 6 a 14 átomos de carbono, heteroarileno de 2 a 13 átomos de carbono, cicloalquileno de 3 a 8 átomos de carbono, hetero-cicloalquileno de 2 a 14 átomos de carbono o alcoxileno de 1

a 8 átomos de carbono, cada uno de los cuales está opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-OC(O)R^9$, alcoxilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, y alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno;

R^5 es arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, $-N(R^9)_2$, $-N(R^9)C(O)R^9$, $-C(O)N(R^9)_2$, $-(CH_2)_pOR^9$ u $-OR^9$;

R^6 es arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, $-OCH(R^7)_2$, $-C(O)R^7$, alquilo de 1 a 8 átomos de carbono, o cicloalquilo de 3 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, y hetero-cicloalquilo de 2 a 14 átomos de carbono de R^6 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, $-CN$,$-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^8$, $OC(O)N(R^4)_2$, $-N(R^9)_2$, $-C(O)C(O)OR^9$, $-(CH_2)_pN(R^9)_2$, $-N(R^4)_2$, $-C(O)N$

$(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-(CH_2)_pS(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-NR^4S(O)_2R^9$, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, alqueno de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por hidroxilo, alquilo de 1 a 8 átomos de carbono sustituido por halógeno y alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno;

o R^6 es arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono o cicloalquilo de 3 a 8 átomos de carbono que tiene un puente de alquilo de 1 a 4 átomos de carbono;

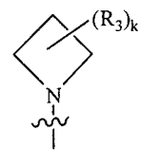
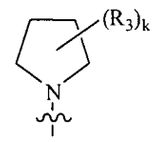
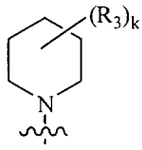
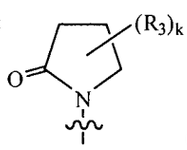
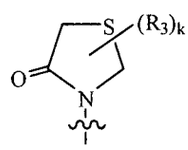
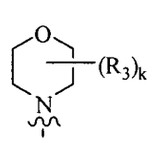
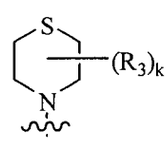
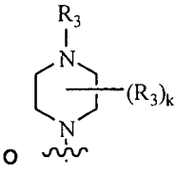
o R^6 es un hetero-cicloalquilo de 2 a 14 átomos de carbono opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, =O, -CN, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^8$, $OC(O)N(R^4)_2$, $-N(R^9)_2$, $-C(O)C(O)OR^9$, $-(CH_2)_pN(R^9)_2$, $-N(R^4)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-(CH_2)_pS(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-NR^4S(O)_2R^9$, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, alqueno de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por hidroxilo, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, y alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno;

cada R^7 se selecciona independientemente a partir de H, alquilo de 1 a 8 átomos de carbono y $-L^1R^8$;

R^8 es H, $-N(R^9)_2$, $-N(R^4)_2$, $-SR^9$, -CN, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono y hetero-cicloalquilo de 2 a 14 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono y hetero-cicloalquilo de 2 a 14 átomos de carbono de R^8 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, alquilo de 1 a 6 átomos de carbono, $-CN$, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-N(R^9)_2$, $-N(R^4)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, y $-NR^4S(O)_2$;

cada R^9 se selecciona independientemente a partir de H, cicloalquilo de 3 a 8 átomos de carbono y alquilo de 1 a 8 átomos de carbono; y

cada p es independientemente 1, 2, 3, 4, 5 ó 6.

En ciertas modalidades, R^1 es  ,  ,  ,  o  , mientras que en otras modalidades, R^1 es  ,  o  .

En ciertas modalidades, cada R^3 se selecciona independientemente a partir de halógeno, $-OR^9$, alquilo de 1 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono y heteroarilo de 2 a 13 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono y heteroarilo de 2 a 13 átomos de carbono de R^3 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hidroxilo, $-OR^9$, alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno y cicloalquilo de 3 a 8 átomos de carbono.

En ciertas modalidades, el arilo de 6 a 14 átomos de carbono de R^3 es fenilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, alquilo de 1 a 8 átomos de carbono, y alquilo de 1 a 8 átomos de carbono sustituido por halógeno.

En ciertas modalidades, el arilo de 6 a 14 átomos de carbono de R^3 es fenilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de flúor y alquilo de 1 a 8 átomos de carbono.

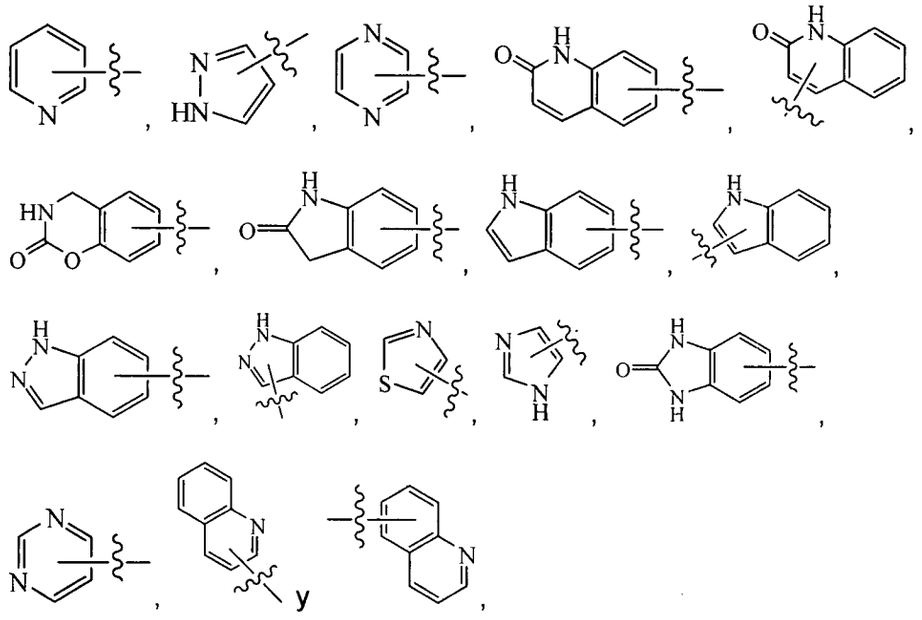
En ciertas modalidades, R^2 es arilo de 6 a 14 átomos de carbono, o heteroarilo de 2 a 13 átomos de carbono, en donde el arilo de 6 a 14 átomos de carbono, y heteroarilo de 2 a 13 átomos de carbono de R^2 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-OC(O)R^9$, alcoxilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno y alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno.

En ciertas modalidades, R^2 es arilo de 6 a 14 átomos de carbono, o heteroarilo de 2 a 13 átomos de carbono, en donde el arilo de 6 a 14 átomos de carbono, y heteroarilo de 2 a 13 átomos de carbono de R^2 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ y $-S(O)_2R^9$.

En ciertas modalidades, el arilo de 6 a 14 átomos de carbono

de R^2 es fenilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ y $-S(O)_2R^9$.

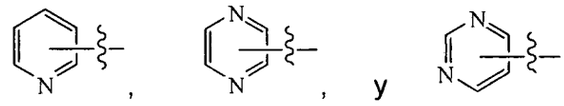
En ciertas modalidades, el heteroarilo de 2 a 13 átomos de carbono de R^2 se selecciona a partir de:



en donde cada uno está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$,

$-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ y $-S(O)_2R^9$.

En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), el heteroarilo de 2 a 13 átomos de carbono de R^2 se selecciona a partir de:

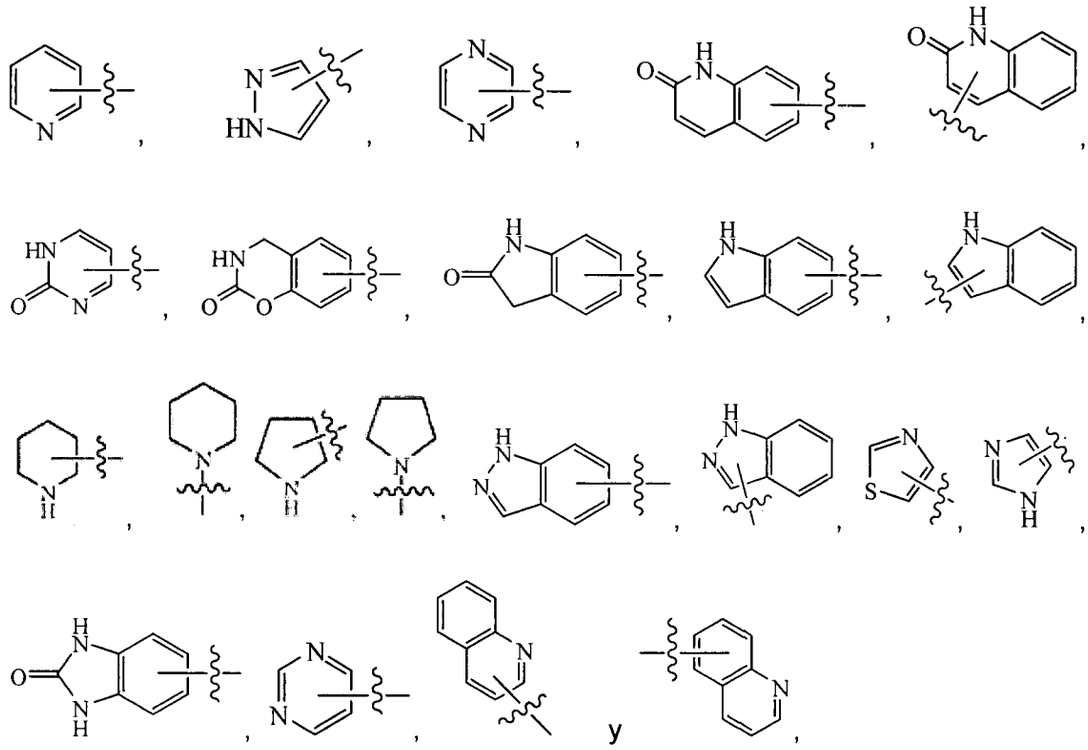


en donde cada uno está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ y $-S(O)_2R^9$.

En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), R^6 es heteroarilo de 2 a 13 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, $-OCH(R^7)_2$, alquilo de 1 a 8 átomos de carbono, o cicloalquilo de 3 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, y hetero-cicloalquilo de 2 a 14 átomos de carbono de R^6 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de $-CN$, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4C(O)R^4$, $-N(R^4)_2$, $-S(O)_2R^9$, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2

a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, alqueno de 2 a 8 átomos de carbono, y alquilo de 1 a 8 átomos de carbono sustituido por hidroxilo.

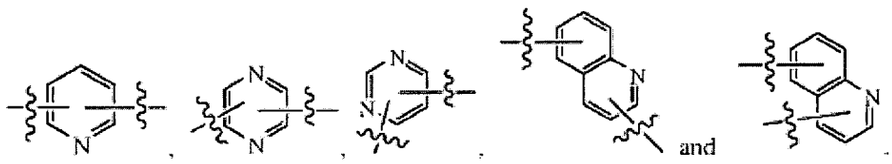
En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), R^6 se selecciona a partir de:



en donde cada uno está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, -CN, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-N(R^4)_2$, $-S(O)_2R^9$, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de

carbono, alqueno de 2 a 8 átomos de carbono, y alquilo de 1 a 8 átomos de carbono sustituido por hidroxilo.

En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), Y^1 es arileno de 6 a 14 átomos de carbono o hetero-arileno de 2 a 13 átomos de carbono, mientras que en otras modalidades, Y^1 se selecciona a partir de:



En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), cada R^4 se selecciona independientemente a partir de H, alquilo de 1 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, $-L^1R^5$, $-L^1R^6$, y cicloalquilo de 3 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, y cicloalquilo de 3 a 8 átomos de carbono están opcionalmente sustituidos con $-(CH_2)_pOR^9$.

En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), R^5 es arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, $-N(R^9)_2$, $-N(R^9)C(O)R^9$, $-(CH_2)_pOR^9$, u $-OR^9$.

En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), R^7 es $-L^1R^8$. En ciertas modalidades de los compuestos anteriormente mencionados de la fórmula (I), R^8 es $-N(R^9)_2$ o $-CN$.

Los compuestos, sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, y composiciones farmacéuticas proporcionadas en la presente, también incluyen todas las variaciones isotópicas adecuadas de estos compuestos, y las sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, y las composiciones farmacéuticas. Una variación isotópica de un compuesto de la invención o una sal farmacéuticamente aceptable del mismo se define como una en donde cuando menos un átomo es reemplazado por un átomo que tiene el mismo número atómico pero una masa atómica diferente de la masa atómica usualmente encontrada en la naturaleza. Los ejemplos de los isótopos que se pueden incorporar en los compuestos de la invención y las sales farmacéuticamente aceptables de los mismos incluyen, pero no se limitan a, 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 de la invención y las sales farmacéuticamente aceptables de los mismos, por ejemplo, aquéllos en donde se incorpora un isótopo radioactivo, tal como ^{3}H o ^{14}C, son útiles en los estudios de distribución de fármacos y/o de sustratos en el tejido. En los ejemplos particulares, se pueden utilizar los isótopos ^{3}H y ^{14}C por

su facilidad de preparación y detectabilidad. En otros ejemplos, la sustitución con isótopos, tales como ^{2}H, puede proporcionar ciertas ventajas terapéuticas que resultan de la mayor estabilidad metabólica, tales como una mayor vida media *in vivo* o requerimientos de dosificación reducida. Las variaciones isotópicas de los compuestos, y las sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, y las composiciones farmacéuticas proporcionadas en la presente, se preparan mediante procedimientos convencionales utilizando las variaciones isotópicas apropiadas de los reactivos adecuados. Las variaciones isotópicas de los compuestos tienen el potencial para cambiar el destino metabólico de un compuesto y/o para crear pequeños cambios en las propiedades físicas, tales como la hidrofobicidad, y similares. La variación isotópica tiene el potencial para mejorar la eficacia y la seguridad, para mejorar la bidisponibilidad y la vida media, para alterar el enlace de proteína, para cambiar la biodistribución, para aumentar la proporción de metabolitos activos, y/o para disminuir la formación de metabolitos reactivos o tóxicos.

Procesos para la elaboración de los compuestos de la fórmula (I)

Los procedimientos generales para la preparación de los compuestos de la fórmula (I) se describen en los Ejemplos que se encuentran más adelante. En las reacciones descritas, se pueden proteger los grupos funcionales reactivos, por ejemplo, los grupos hidroxilo, amino, imino, tio, o carboxilo, en donde se deseen éstos en

el producto final, para evitar su participación indeseada en las reacciones. Se pueden utilizar los grupos protectores convencionales de acuerdo con la práctica estándar (véase, por ejemplo, T.W. Greene y P. G. M. Wuts en "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991).

En ciertas modalidades, los compuestos de la fórmula (I) descritos en la presente se preparan como una sal de adición de ácido farmacéuticamente aceptable, mediante la reacción de la forma de base libre del compuesto de la fórmula (I) con un ácido orgánico o un ácido inorgánico farmacéuticamente aceptable. En otras modalidades, una sal de adición de base farmacéuticamente aceptable de los compuestos de la fórmula (I) descritos en la presente, se prepara mediante la reacción de la forma del ácido libre del compuesto de la fórmula (I) con una base orgánica o una base inorgánica farmacéuticamente aceptable. De una manera alternativa, las formas de sal de los compuestos de la fórmula (I) descritos en la presente, se preparan utilizando sales de los materiales de partida o intermediarios. En ciertas modalidades, los compuestos de la fórmula (I) descritos en la presente están en la forma de otras sales, incluyendo, pero no limitándose a, oxalatos y trifluoro-acetatos. En ciertas modalidades, se forman hemi-sales de ácidos y bases, por ejemplo, sales de hemisulfato y de hemicalcio.

Los ácidos orgánicos o los ácidos inorgánicos farmacéuticamente aceptables utilizados para formar las sales de adición de ácido farmacéuticamente aceptables de los compuestos

de la fórmula (I) incluyen, pero no se limitan a, ácido fluorhídrico, ácido clorhídrico, ácido bromhídrico, ácido yodhídrico, ácido nítrico, ácido sulfúrico, ácido fosfórico, ácido fórmico, ácido acético, ácido trifluoro-acético, ácido propiónico, ácido butírico, ácido caprílico, ácido dicloro-acético, ácido hipúrico, ácido láctico, ácido cítrico, ácido tartárico, ácido málico, ácido glucónico, ácido mandélico, ácido maleico, ácido succínico, ácido adípico, ácido aspártico, ácido fumárico, ácido glutámico, ácido malónico, ácido sebácico, ácido salicílico, ácido hexanoico, ácido benzoico, ácido p-cloro-benzoico, ácido nicotínico, ácido difenil-acético, ácido trifenil-acético, ácido o-hidroxi-benzoico, ácido p-hidroxi-benzoico, ácido 1-hidroxi-naftalen-2-carboxílico ó ácido 3-hidroxi-naftalen-2-carboxílico, los ácidos sulfónicos, ácido metan-sulfónico, ácido bencen-sulfónico, ácido etan-sulfónico, ácido etan-1,2-disulfónico, ácido 2-hidroxi-etan-sulfónico, (+)-ácido canfor-10-sulfónico, ácido naftalen-2-sulfónico, ácido naftalen-1,5-disulfónico y ácido p-toluen-sulfónico. Los solvatos farmacéuticamente aceptables son en términos generales los hidratos.

Las sales de adición de ácido farmacéuticamente aceptables de los compuestos de la fórmula (I) incluyen, pero no se limitan a, una sal de bromhidrato, clorhidrato, sulfato, nitrato, succinato, maleato, formato, acetato, adipato, besilato, bicarbonato/carbonato, propionato, fumarato, citrato, tartrato, lactato, benzoato, salicilato, glutamato, aspartato, p-toluen-sulfonato, bencen-sulfonato, metan-sulfonato, etan-sulfonato, naftalen-sulfonato (por ejemplo, 2-

naftalen-sulfonato), hexanoato, o sales de bisulfato/sulfato, borato, camsilato, ciclamato, edisilato, esilato, gluceptato, gluconato, glucuronato, hexafluoro-fosfato, hibenzato, clorhidrato/cloruro, bromhidrato/bromuro, yodhidrato/yoduro, isetionato, lactato, malato, malonato, mesilato, metil-sulfato, naftilato, 2-napsilato, nicotinato, orotato, oxalato, palmitato, pamoato, fosfato/fosfato fosfato ácido/diácido, piroglutamato, sacarato, estearato, tanato, tosilato, trifluoro-acetato y xinofoato.

Las sales de adición de base farmacéuticamente aceptables de un compuesto de la fórmula (I) incluyen, pero no se limitan a, las sales de aluminio, amonio, arginina, benzatina, calcio, colina, dietil-amina, diolamina, glicina, lisina, magnesio, meglumina, olamina, potasio, sodio, trometamina, etanolaminas, bencil-aminas, piridina, benetamina, dietanolamina, 4-(2-hidroxi-etil)-morfolina, 1-(2-hidroxi-etil)-pirrolidina, N-metil-glutamina, piperazina, trietanol-amina y zinc.

En ciertas modalidades, las formas del ácido libre o de base libre de los compuestos de la fórmula (I) descritos en la presente, se preparan a partir de la forma de sal de adición de base o de sal de adición de ácido correspondiente, respectivamente. Por ejemplo un compuesto fórmula (I) en una forma de sal de adición de ácido se convierte hasta la base libre correspondiente mediante el tratamiento con una base adecuada (a manera de ejemplo solamente, una solución de hidróxido de amonio, de hidróxido de sodio, y similares). Por ejemplo, un compuesto de la fórmula (I) en una forma de sal de adición de base se convierte hasta el ácido libre correspondiente

mediante el tratamiento con un ácido adecuado (a manera de ejemplo solamente, ácido clorhídrico).

En ciertas modalidades, los compuestos de la fórmula (I) descritos en la presente, en una forma no oxidada, se preparan a partir de los N-óxidos de los compuestos fórmula (I) mediante el tratamiento con un agente reductor (a manera de ejemplo solamente, azufre, dióxido de azufre, trifenil-fosfina, borohidruro de litio, borohidruro de sodio, tricloruro de fósforo, tribromuro, o similares), en un solvente orgánico inerte adecuado (a manera de ejemplo solamente, acetonitrilo, etanol, dioxano acuoso, o similares) de 0°C a 80°C.

En ciertas modalidades, se preparan derivados de pro-fármaco de los compuestos fórmula (I) descritos en la presente, empleando los métodos conocidos por aquéllos de una experiencia ordinaria en este campo (por ejemplo, para mayores detalles, véase Saulnier y colaboradores (1994), Bioorganic and Medicinal Chemistry Letters, Volumen 4, página 1985). Por ejemplo, los pro-fármacos apropiados se preparan mediante la reacción de un compuesto no derivado de la fórmula (I) con un agente carbamilante adecuado (a manera de ejemplo solamente, 1,1-aciloxi-alquil-carbano-cloridato, carbonato de para-nitro-fenilo, o similares).

En ciertas modalidades, los compuestos de la fórmula (I) descritos en la presente, se preparan como derivados protegidos empleando los métodos conocidos por aquéllos de una experiencia ordinaria en este campo. Se puede encontrar una descripción

detallada de las técnicas aplicables a la creación de los grupos protectores y su remoción en T. W. Greene, "Protecting Groups in Organic Chemistry," 3ª Edición, John Wiley and Sons, Inc., 1999.

En ciertas modalidades, los compuestos de la fórmula (I) descritos en la presente, se preparan o se forman como solvatos (por ejemplo, hidratos). En ciertas modalidades, se preparan hidratos de los compuestos de la fórmula (I) mediante recristalización a partir de una mezcla de solventes acuosos/orgánicos, utilizando solventes orgánicos, tales como dioxina, tetrahidrofurano, o metanol.

En ciertas modalidades, los compuestos de la fórmula (I) proporcionados en la presente, se preparan como una mezcla racémica. En ciertas modalidades, los compuestos de la fórmula (I) descritos en la presente, se preparan como sus estereoisómeros individuales. En ciertas modalidades, los compuestos de la fórmula (I) proporcionados en la presente, se preparan como una mezcla racémica, y sus estereoisómeros individuales se obtienen utilizando cromatografía quiral, incluyendo, pero no limitándose a, cromatografía quiral de líquidos. En otras modalidades, los compuestos de la fórmula (I) descritos en la presente, se preparan como sus estereoisómeros individuales mediante la reacción de una mezcla racémica del compuesto con un agente de resolución ópticamente activo para formar un par de compuestos diaestereoisoméricos, se separan los diaestereómeros, y se recuperan los enantiómeros ópticamente puros. En ciertas modalidades, la resolución de los enantiómeros se lleva a cabo

utilizando derivados diaestereoméricos covalentes de los compuestos de la fórmula (I), o mediante la utilización de complejos disociables (por ejemplo, sales diaestereoméricas cristalinas). Los diaestereómeros tienen distintas propiedades físicas (por ejemplo, puntos de fusión, puntos de ebullición, solubilidad, reactividad, etc.), y se separan fácilmente aprovechando estas diferencias. En ciertas modalidades, los diaestereómeros se separan mediante cromatografía, o mediante técnicas de separación/resolución, basándose en las diferencias en la solubilidad. Entonces se recupera el enantiómero ópticamente puro, junto con el agente de resolución, por cualquier medio práctico que no dé como resultado la racemización. Se puede encontrar una descripción más detallada de las técnicas aplicables a la resolución de estereoisómeros de los compuestos a partir de su mezcla racémica en Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley and Sons, Inc., 1981.

Los compuestos de la fórmula (I) se proporcionan en una forma sustancialmente pura. En ciertas modalidades, los compuestos de la fórmula (I) son cuando menos el 60 por ciento puros. En ciertas modalidades, los compuestos de la fórmula (I) son cuando menos el 75 por ciento puros. En ciertas modalidades, los compuestos de la fórmula (I) son cuando menos el 85 por ciento puros. En ciertas modalidades, los compuestos de la fórmula (I) son cuando menos el 98 por ciento puros (los porcentajes son sobre una base de peso por peso).

Los compuestos de la fórmula (I) se hacen mediante los procesos descritos en la presente, y como se ilustra en los Ejemplos. En ciertas modalidades, los compuestos de la fórmula (I) se hacen mediante:

(a) opcionalmente convertir un compuesto de la invención en una sal farmacéuticamente aceptable;

(c) opcionalmente convertir una forma de sal de un compuesto de la invención hasta una forma no de sal;

(d) opcionalmente convertir una forma no oxidada de un compuesto de la invención hasta un N-óxido farmacéuticamente aceptable;

(e) opcionalmente convertir una forma de N-óxido de un compuesto de la invención hasta su forma no oxidada;

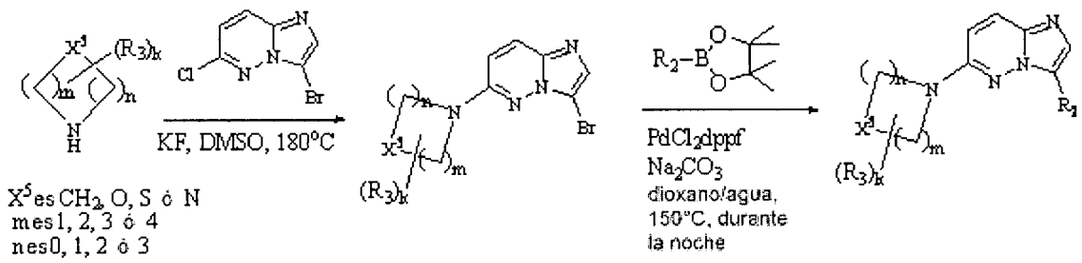
(f) opcionalmente resolver un isómero individual de un compuesto de la invención a partir de una mezcla de isómeros;

(g) opcionalmente convertir un compuesto no derivado de la invención hasta un derivado de pro-fármaco farmacéuticamente aceptable; y

(h) opcionalmente convertir un derivado de pro-fármaco de un compuesto de la invención hasta su forma no derivada.

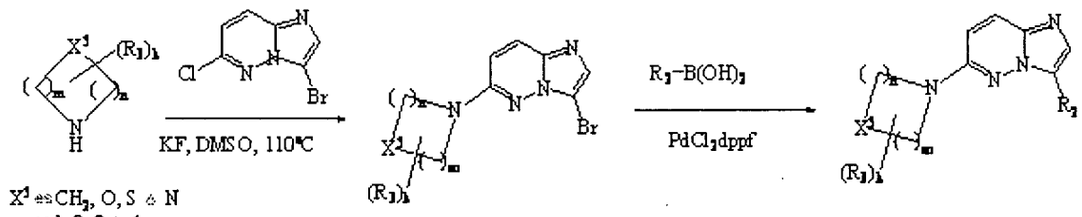
Los ejemplos no limitantes de los esquemas sintéticos utilizados para la elaboración de los compuestos de la fórmula (I) descritos en la presente, se ilustran en los esquemas de reacción (I) a (V), en donde n, m, k, X^5, R^2 y R^3 son como se definen en la presente.

Esquema de Reacción (I)



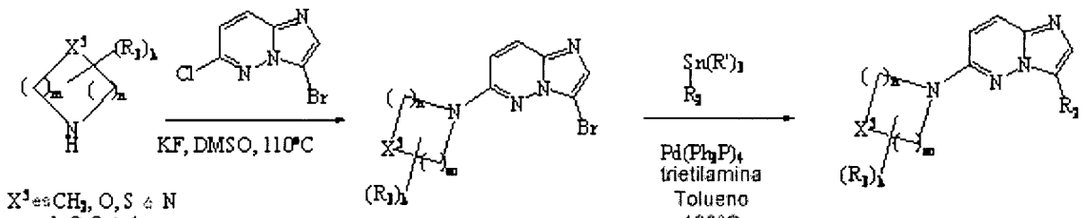
X^5 es CH_2, O, S ó N
mes 1, 2, 3 ó 4
nes 0, 1, 2 ó 3

Esquema de Reacción (II)



X^1 es CH_2, O, S ó N
mes 1, 2, 3 ó 4
nes 0, 1, 2 ó 3

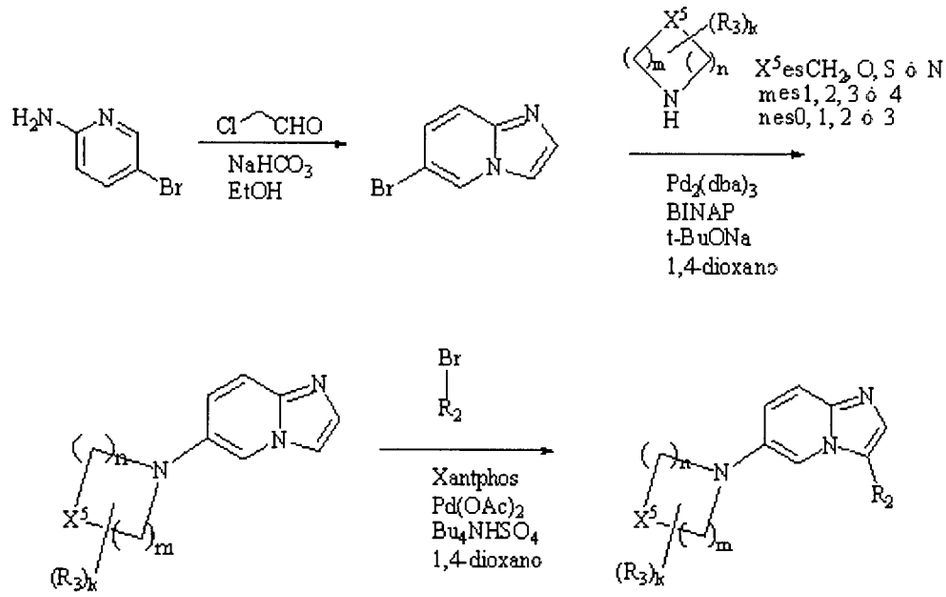
Esquema de Reacción (III)



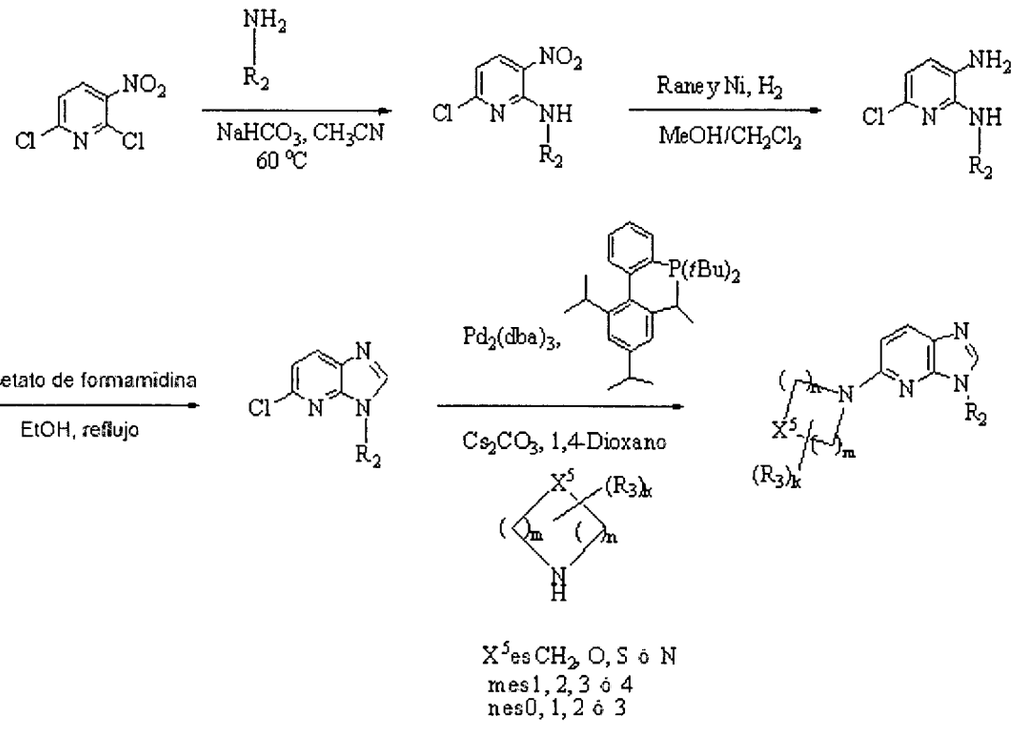
X^1 es CH_2, O, S ó N
mes 1, 2, 3 ó 4
nes 0, 1, 2 ó 3

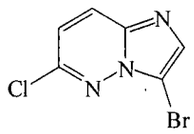
R' es alquilo C_1 - C_6

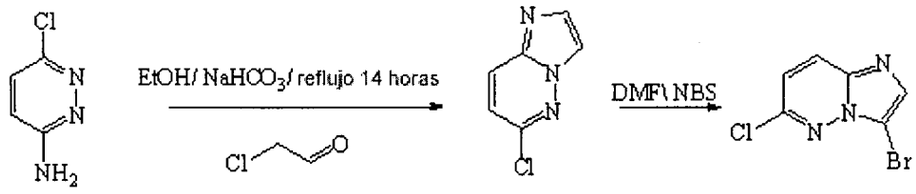
Esquema de Reacción (IV)



Esquema de Reacción (V)



En seguida se muestra un ejemplo no limitante de la síntesis del Intermediario  :



Farmacología y Utilidad

Las cinasas de proteína (PTK) tienen una función central en la regulación de una amplia variedad de procesos celulares, y en el mantenimiento del control sobre la función celular. Las cinasas de proteína catalizan y regulan el proceso de fosforilación, en donde las cinasas unen covalentemente los grupos fosfato a los objetivos de proteínas o de lípidos en respuesta a una variedad de señales extracelulares. Los ejemplos de estos estímulos incluyen hormonas, neurotransmisores, factores de crecimiento y diferenciación, eventos del ciclo celular, tensiones medio-ambientales y tensiones nutricionales. Un estímulo extracelular puede afectar a una o más respuestas celulares relacionadas con el crecimiento celular, migración, diferenciación, secreción de hormonas, activación de factores de transcripción, contracción muscular, metabolismo de glucosa, control de la síntesis de proteínas, y regulación del ciclo

celular.

Muchas enfermedades están asociadas con respuestas celulares anormales desencadenadas por los eventos mediados por la cinasa de proteína. Estas enfermedades incluyen, pero no se limitan a, enfermedades autoinmunes, enfermedades inflamatorias, enfermedades óseas, enfermedades metabólicas, enfermedades neurológicas y neurodegenerativas, cáncer, enfermedades cardiovasculares, enfermedades respiratorias, alergias y asma, enfermedad de Alzheimer, y enfermedades relacionadas con hormonas.

Los ejemplos de las cinasas de proteína tirosina incluyen, pero no se limitan a:

(a) cinasas de tirosina, tales como Irk, IGFR-1, Zap-70, Bmx, Btk, CHK (cinasa homóloga de Csk), CSK (cinasa Src C-terminal), Itk-1, Src (c-Src, Lyn, Fyn, Lck, Syk, Hck, Yes, Blk, Fgr, y Frk), Tec, Txk/Rlk, Abl, EGFR (EGFR-1/ErbB-1, ErbB-2/NEU/HER-2, ErbB-3, y ErbB-4), FAK, FGF1R (también FGFR1 o FGR-1), FGF2R (también FGR-2), MET (también Met-I o c-MET), PDGFR (α y ß), Tie-1, Tie-2 (también Tek-1 o Tek), VEGFR1 (también FLT-1), c-FMS, VEGFR2 (también KDR), FLT-3, FLT-4, c-KIT, JAK1, JAK2, JAK3, TYK2, LOK, RET, Ros, TRKA, TRKB, TRKC, PYK2, ALK (Cinasa de Linfoma Anaplásico), EPHA (1-8), EPHB (1-6), RON, Fes, Fer, o EPHB4 (también EPHB4-1), y

(b) cinasas de serina/treonina, tales como Aurora, c-RAF, SGK, cinasas MAP (por ejemplo, MKK4, MKK6, etc.), SAPK2α,

SAPK2β, Ark, ATM (1-3), CamK (1-IV), CamKK, Chk1 y 2 (cinasas Checkpoint), CKI, CK2, Erk, IKK-I (también IKK-ALFA o CHUK), IKK-2 (también IKK-BETA), Ilk, Jnk (1-3), LimK (1 y 2), MLK3Raf (A, B, y C), CDK (1-10), PKC (incluyendo todos los subtipos de PKC), Plk (1-3), NIK, Pak (1-3), PDK1, PKR, RhoK, RIP, RIP-2, GSK3 (α y ß), PKA, P38, Erk (1-3), PKB (incluyendo todos los subtipos de PKB) (también AKT-1, AKT-2, AKT-3, o AKT3-1), IRAK1, FRK, SGK, TAK1 y Tp1-2 (también COT).

La fosforilación modula o regula una variedad de procesos celulares, tales como proliferación, crecimiento, diferenciación, metabolismo, apoptosis, movilidad, transcripción, traducción y otros procesos de señalización. Se ha observado una actividad aberrante o excesiva de PTK en muchos estados de enfermedad, incluyendo, pero no limitándose a, trastornos proliferativos benignos y malignos, enfermedades resultantes de una activación inapropiada del sistema inmune, y enfermedades resultantes de una activación inapropiada del sistema nervioso. Las enfermedades y condiciones de enfermedad específicas incluyen, pero no se limitan a, trastornos autoinmunes, rechazo de aloinjerto, enfermedad del injerto contra el huésped, retinopatía diabética, neovascularización coroidal debida a degeneración macular relacionada con la edad, soriasis, artritis, osteoartritis, artritis reumatoide, invasión de pannus sinovial en artritis, esclerosis múltiple, miastenia grave, obesidad, diabetes mellitus, angiopatía diabética, retinopatía de prematuridad, hemangiomas infantiles, cáncer pulmonar no microcelular, de vejiga,

y de cabeza y cuello, cáncer de próstata, cáncer de mama, cáncer de ovario, cáncer gástrico y pancreático, soriasis, fibrosis, artritis reumatoide, ateroesclerosis, restenosis, enfermedad auto-inmune, alergia, enfermedades respiratorias, asma, rechazo de trasplante, inflamación, trombosis, proliferación de los vasos retinales, enfermedad inflamatoria del intestino, enfermedad de Crohn, colitis ulcerativa, enfermedades óseas, rechazo de trasplante o rechazo de trasplante de médula ósea, lupus, pancreatitis crónica, caquexia, choque séptico, enfermedades o trastornos fibroproliferativos y diferenciativos de la piel, enfermedades del sistema nervioso central, enfermedades neurodegenerativas, trastornos o condiciones relacionadas con daño de nervios y degeneración de axones después de lesión de cerebro o de la médula espinal, cáncer agudo o crónico, enfermedades oculares, infecciones virales, enfermedad cardíaca, enfermedades del pulmón o pulmonares, o enfermedades del riñón o renales, y bronquitis.

Las cinasas de tirosina se pueden clasificar ampliamente como cinasas de proteína tirosina de tipo receptor (que tienen dominios extracelulares, transmembrana, e intracelulares), o de tipo no receptor (que son completamente intracelulares). La activación inapropiada o incontrolada de muchas de estas cinasas (actividad aberrante de la cinasa de proteína tirosina), por ejemplo, por una sobre-expresión o mutación, da como resultado un crecimiento celular incontrolado. Se ha encontrado que muchas de las cinasas de proteína tirosina, ya sean cinasas de tirosina receptoras o no

receptoras, están involucradas en las sendas de señalización celular involucradas en numerosas condiciones patogénicas, incluyendo, pero no limitándose a, inmunomodulación, inflamación, o trastornos proliferativos, tales como cáncer.

Los compuestos de la invención se rastrean contra un panel de cinasas (de tipo silvestre y/o mutaciones de las mismas), y modulan la actividad de cuando menos un miembro del panel de cinasas. Los ejemplos de las cinasas que son inhibidas por los compuestos y composiciones farmacéuticas que se proporcionan en la presente, y contra las cuales son útiles los métodos descritos en la presente incluyen, pero no se limitan a, Ros, KDR, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, las cinasas de proteína TrkA, TrkB, TrkC, IGF-1R, y/o ALK, y las formas mutantes de las mismas. Como tales, los compuestos y composiciones farmacéuticas proporcionadas en la presente son útiles para el tratamiento de las enfermedades o trastornos en donde estas cinasas contribuyan a la patología y/o sintomatología de una enfermedad o trastorno asociado con tales cinasas. Estas enfermedades o trastornos incluyen, pero no se limitan a, cáncer pancreático, carcinoma papilar de tiroides, carcinoma de ovario, carcinoma quístico de adenoides humanas, cáncer pulmonar no microcelular, carcinoma de mama secretor, fibrosarcoma congénito, nefroma mesoblástico congénito, leucemia mielógena aguda, soriasis, metástasis, dolor relacionado con cáncer, y neuroblastoma.

Cinasas de Tirosina Receptoras (RTKs).

Las cinasas de tirosina receptoras (RTKs) comprenden una gran familia de receptores transmembrana con diversas actividades biológicas. Se ha identificado un número de sub-familias de RTK distintas, incluyendo, pero no limitándose a, la familia de receptores ALK, la familia de receptores del factor de crecimiento epidérmico (EGF), la familia de receptores de insulina, la familia de receptores del factor de crecimiento derivado de plaquetas (PDGF), la familia de receptores de FGF, la familia de receptores del factor de crecimiento endotelial vascular (VEGF), la familia de receptores de HGF, la familia de receptores Trk, la familia de receptores EPH, la familia de receptores AXL, la familia de receptores LTK, la familia de receptores TIE, la familia de receptores ROR, la familia de receptores DDR, la familia de receptores RET, la familia de receptores KLG, la familia de receptores RYK, y la familia de receptores MuSK.

Se ha demostrado que las cinasas de tirosina receptoras no solamente son reguladores clave de los procesos celulares normales, sino que también tienen una función crítica en el desarrollo y progreso de muchos tipos de cáncer. La familia de cinasas de tirosina receptoras (RTK) incluye receptores que son cruciales para el crecimiento y la diferenciación de una variedad de tipos de células. La función intrínseca de la transducción de señales mediada por RTK es iniciada por la interacción extracelular con un factor de

crecimiento específico (ligando), típicamente seguida por la dimerización del receptor, el estímulo de la actividad intrínseca de la cinasa de proteína tirosina, y la trans-fosforilación del receptor. De esta manera se crean sitios de enlace para las moléculas de transducción de señales intracelulares, y conducen a la formación de complejos con un espectro de moléculas de señalización citoplásmica que facilitan la respuesta celular apropiada, tal como, a manera de ejemplo solamente, la división celular, la diferenciación, los efectos metabólicos, y los cambios en el micro-medio ambiente extracelular.

Familia de Cinasa Receptora de Tropomiosina (Trk)

Las cinasas de tirosina receptoras de la familia Trk (genes NTRK), TrkA (NTRK1), TrkB (NTRK2), y TrkC (NTRK3), son los receptores de señalización que median las acciones biológicas de las hormonas peptídicas de la familia de neurotrofina. Los receptores Trk son receptores enlazados con membrana que, a través de varias cascadas de señales, controlan el crecimiento y la sobrevivencia neuronal, y la diferenciación, migración y metástasis de las células tumorales. La familia de factores de crecimiento de neurotrofina incluye al factor de crecimiento de nervios (NGF), al factor neurotrófico derivado de cerebro (BDNF), y dos neurotrofinas (NT), NT-3 y NT-4. Las neurotrofinas son críticas para el funcionamiento del sistema nervioso, y la activación de los receptores Trk mediante el enlace de neurotrofina conduce a la activación de las cascadas de señales que dan como resultado la promoción de la sobrevivencia y

otra regulación funcional de las células. Cada tipo de neurotrofina tiene una afinidad de enlace diferente hacia su receptor Trk correspondiente, y sobre el enlace de la neurotrofina, los receptores Trk se fosforilan ellos mismos y a los miembros de la senda de MAPK. Las diferencias en la señalización iniciada por estos distintos tipos de receptores son importantes para la generación de diversas respuestas biológicas.

Los receptores de cinasa de la familia Trk promueven la tumorigénesis y son capaces de controlar el crecimiento y la sobrevivencia de las células tumorales, así como su diferenciación, migración y metástasis. Los receptores Trk están implicados en el desarrollo y progreso de cáncer, a través de la sobre-regulación ya sea del receptor, de su ligando (NGF) (BDNF, NT-3, y NT-4), o ambos. En muchos casos, la alta expresión de Trk está asociada con un comportamiento tumoral agresivo, con un pronóstico pobre, y con metástasis. Por consiguiente, las enfermedades y trastornos relacionados con los receptores Trk resultan a partir de: 1) la expresión de los receptores Trk en células que normalmente no expresan estos receptores; 2) la expresión de los receptores Trk por parte de las células que normalmente no expresan estos receptores; 3) la expresión aumentada de los receptores Trk, que conduce a una proliferación celular indeseada; 4) la expresión aumentada de los receptores Trk, que conduce a sobrevivencia celular independiente de la adhesión; 5) las mutaciones que conducen a una activación constitutiva de los receptores Trk; 6) el sobre-estímulo de los

receptores Trk, debido a una cantidad anormalmente alta de, o a mutaciones en, los receptores Trk, y/o 7) una cantidad anormalmente alta de la actividad de los receptores Trk, debido a una cantidad anormalmente alta de, o a mutaciones en, los receptores Trk.

Se han encontrado anormalidades genéticas, es decir, mutaciones puntuales y reconfiguraciones cromosómicas que involucran a ambos genes que expresan TrkB y TrkC, en una variedad de tipos de cáncer. En un planteamiento cinomérico para identificar mutantes puntuales en cinasas de tirosina, se encontraron mutaciones en los genes que expresan TrkB y TrkC en las líneas celulares y en las muestras primarias de los pacientes con cáncer colo-rectal. En adición, se han encontrado translocalizaciones cromosómicas que involucran TrkA y TrkB, en varios tipos diferentes de tumores. Las reconfiguraciones genéticas que involucran a los genes que expresan TrkA y un conjunto de diferentes componentes de fusión (TPM3, TPR, TFG) son una indicación de un subconjunto de cánceres papilares de tiroides. Más aún, se ha demostrado que el cáncer de mama secretor, el fibrosarcoma infantil, y el nefroma mesoblástico congénito están asociados con una reconfiguración cromosómica t(12;15) que genera un gen de fusión ETV6-NTRK3 que se mostró que tiene actividad de cinasa constitutiva y un potencial de transformación en varias líneas celulares diferentes, incluyendo fibroblastos, células hematopoiéticas, y células epiteliales de mama.

TrkA tiene la más alta afinidad con el factor de crecimiento de nervios de enlace (NGF). NGF es importante en las acciones tanto

locales como nucleares, y regula el crecimiento de los conos, la movilidad, y la expresión de los genes que codifican las enzimas de biosíntesis para los neurotransmisores. Las neuronas sensoriales nocirreceptivas expresan en su mayor parte TrkA y no TrkB o TrkC.

TrkB sirve como un receptor tanto para BDNF como para NT-4, y se expresa en las células de tipo neuroendocrino en el intestino delgado y en el colon, en las células alfa del páncreas, en los monocitos y macrófagos de los nodos linfáticos y del bazo, y en las capas granulares de la epidermis. TrkB también se expresa en las células cancerosas de próstata pero no en las células normales.

El enlace de BDNF con el receptor TrkB provoca la activación de las cascadas intercelulares que regulan el desarrollo y plasticidad neuronal, el potenciamiento a largo plazo, y la apoptosis. BDNF promueve la proliferación, diferenciación, y crecimiento y sobrevivencia de los componentes neurales normales, tales como las células retinales y las células gliales. En adición, la activación de TrkB es un supresor potente y específico de la muerte celular independiente del anclaje (anoikis), el cual es inducido por la apoptosis por la pérdida de unión de una célula a su matriz. A manera de ejemplo, la activación del eje de señalización de la cinasa de fosfatidil-inositol/cinasa B de proteína mediante TrkB promueve la sobrevivencia de las células epiteliales no transformadas en los cultivos tridimensionales, e induce la formación de tumor y metástasis de estas células en los ratones inmuno-comprometidos. La sobrevivencia celular independiente del anclaje es un proceso

metastásico que permite que las células tumorales migren a través de la circulación sistémica y crezcan en los órganos distantes. El agonismo de TrkB da como resultado el fracaso de la muerte celular inducida por los tratamientos de cáncer. Por consiguiente, la modulación de TrkB es un objetivo para el tratamiento de las enfermedades proliferativas benignas y malignas, en especial de las enfermedades tumorales.

Las enfermedades y trastornos relacionados con el receptor TrkB incluyen, pero no se limitan a, cánceres, tales como, a manera de ejemplo solamente, progreso de neuroblastoma, progreso de tumor de Wilm, cáncer de mama, cáncer pancreático, cáncer de colon, cáncer de próstata, y cáncer de pulmón. Se ha demostrado que el receptor TrkB está asociado con la enfermedad de Alzheimer.

La investigación adicional ha descubierto mutaciones en TrkB en los seres humanos, que da como resultado una pérdida parcial de la actividad enzimática del receptor. Esta legión genética da como resultado un aumento en el apetito y en la obesidad (obesidad hiperfágica). Se han obtenido resultados similares en los modelos de ratón, reforzando por consiguiente la hipótesis de que la disminución de la actividad de TrkB podría servir para modular el comportamiento de la alimentación, y sería útil en el tratamiento de trastornos tales como anorexia.

Otras indicaciones no oncológicas para un inhibidor de Trk incluyen dermatitis atópica y soriasis.

TrkC se activa mediante su enlace con NT-3, y es expresada

por las neuronas sensoriales propioceptivas. Los axones de estas neuronas sensoriales propioceptivas son mucho más gruesos que aquéllos de las neuronas sensoriales nocirreceptivas, que expresan TrkA. La señalización a través de TrkC conduce a la diferenciación celular y al desarrollo de neuronas propioceptivas que detectan la posición corporal. Las mutaciones en este gen que expresa TrkC están asociadas con los meduloblastomas, los carcinomas de mama secretores, y otros cánceres. En adición, la alta expresión de TrkC es una indicación de melanoma, en especial en los casos con metástasis del cerebro.

Los miembros de la familia Trk, en especial NTRK1 y NTRK2, tienen una función en el cáncer pancreático, en donde: i) se ha mostrado una alta expresión de diferentes miembros de la familia Trk y sus ligandos cognados en las muestras de tejido a partir de los pacientes con cáncer pancreático; ii) la sobre-expresión de NTRK2 se ha vinculado con un fenotipo maligno y altamente metastásico de cáncer pancreático; iii) la alta expresión de NTRK1/NGF se ha correlacionado con una mayor proliferación, comportamiento invasivo, y dolor en los pacientes con cáncer pancreático (PC); y iv) se ha demostrado que el factor de crecimiento de nervios aumenta el potencial invasivo de las líneas celulares de cáncer pancreático. La sobre-expresión de TrkA en el cáncer pancreático podría ser causada por la metilación de los sitios AP-1 reguladores negativos en la región del promotor de TrkA.

La reconfiguración de los genes que involucran NTRK1 es una

210

indicación de un sub-conjunto de cánceres papilares de tiroides. Los oncogenes *TRK* específicos de tiroides se generan mediante reconfiguraciones del gen *NTRK1* con tres genes activadores diferentes, es decir, *TPR*, *TPM3*, y *TFG*.

Varias mutaciones de pérdida de función en TrkA son responsables de la insensibilidad congénita al dolor con anhidrosis (CIPA), un trastorno caracterizado por una falta de sensación de dolor y anhidrosis. Más recientemente, se ha demostrado que un anticuerpo de TrkA antagonista es eficaz en los modelos animales de dolor inflamatorio y neuropático. En adición, TrkA y NGF se han implicado en la provocación del dolor relacionado con cáncer. Se demostró que el NGF es secretado por la célula tumoral y los macrófagos invasores de tumores secretan NGF, el cual estimula directamente a la TrkA localizada sobre las fibras periféricas del dolor. Utilizando diferentes modelos de tumor tanto en ratón como en ratas, se demostró que la neutralización del NGF con un anticuerpo monoclonal inhibe el dolor relacionado con cáncer hasta un grado similar o superior a la dosis más alta tolerada de morfina. Por consiguiente, se puede utilizar un inhibidor selectivo de TrkA en el tratamiento del dolor asociado con cáncer.

La alta expresión de las Trks se encuentra en el tumor de Wilm, en el carcinoma de próstata, y en los cánceres pancreáticos. La alta expresión de TrkC es una indicación de carcinoma. En el neuroblastoma, la alta expresión de TRKB está correlacionada con tumores agresivos intratables y con la resistencia a las terapias

citotóxicas convencionales. En los modelos de metástasis de cáncer de ratón, el gen NTRK2 (proteína TrkB) puede inducir metástasis, y la remoción del gen revierte este potencial metastásico. La gran cantidad de evidencia sugiere que la inhibición de las enzimas de Trk bloquearía el crecimiento y la extensión de diversos cánceres en donde esté involucrada la Trk. Adicionalmente, hay mutaciones activadoras presentes en las Trks en el 7 por ciento de los cánceres.

Ciertos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas proporcionadas en la presente son inhibidores de las cinasas de tirosina receptoras Trk (TrkA, TrkB, y TrkC), y por consiguiente, estos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas son útiles para el tratamiento de las enfermedades y/o los trastornos que respondan a la inhibición de las cinasas de tirosina receptoras Trk (TrkA, TrkB, y TrkC). En ciertas modalidades, estos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas son útiles en el tratamiento de cáncer, mediante la inhibición del desarrollo y/o progreso del cáncer. En ciertas modalidades, estos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas son útiles en el tratamiento de las enfermedades y/o los trastornos que incluyen, pero no se limitan a, neuroblastoma, tumor de Wilm, cáncer de mama, cáncer pancreático, cáncer de colon, cáncer de próstata, cáncer de pulmón, melanoma, anorexia, dermatitis atópica, soriasis y enfermedad de Alzheimer.

211

Familia de receptores del factor de crecimiento derivado de plaquetas (PDGF)

El PDGF (factor de crecimiento derivado de plaquetas) es un factor de crecimiento que se presenta muy comúnmente, el cual tiene una función importante tanto en el crecimiento normal como también en la proliferación celular patológica, tal como se ve en la carcinogénesis y en las enfermedades de las células de músculo liso de los vasos sanguíneos, por ejemplo en ateroesclerosis y trombosis. La familia del factor de crecimiento PDGF consiste en PDGF-A, PDGF-B, PDGF-C, y PDGF-D, los cuales forman ya sea homo- o bien hetero-dímeros (AA, AB, BB, CC, DD) que se enlazan con los receptores de cinasa de proteína tirosina PDGFR-α y PDGFR-ß. La dimerización de los factores de crecimiento es un requisito previo para la activación de la cinasa, debido a que las formas monoméricas son inactivas. Las dos isoformas del receptor se dimerizan sobre el enlace, dando como resultado tres posibles combinaciones de receptores, PDGFR-αα, PDGFR-ßß, y PDGFRαß. El factor de crecimiento AA se enlaza solamente con -αα, el factor de crecimiento BB se pueden enlazar con -αα, -ßß y-αß, los factores de crecimiento CC y AB interactúan específicamente con -αα y -αß, y el factor de crecimiento DD se enlaza con -ßß.

Los mediadores clave corriente abajo de la señalización de PDGFR son las sendas de Ras/cinasa de proteína activada por mitógeno (MAPK), cinasa PI-3, y fosfolipasa-γ (PLCγ). Los miembros de la familia MAPK regulan diferentes funciones biológicas mediante

la fosforilación de las moléculas objetivo (factores de transcripción y otras cinasas) y, por consiguiente, contribuyen a la regulación de los procesos celulares, tales como proliferación, diferenciación, apoptosis, e inmuno-respuestas. La PIP3 generada por la activación de la cinasa PI-3, que funciona como un segundo mensajero para activar las cinasas de tirosina corriente abajo Btk e Itk, y las cinasas de serina/treonina PDK1 y Akt (PKB). La activación de Akt está involucrada en la sobrevivencia, proliferación, y crecimiento celular. Después de que la activación, PLCγ hidroliza su sustrato, PtdIns(4,5)P2, y forma dos mensajeros secundarios, diacil-glicerol e Ins(1,4,5)P3 que estimula los procesos intracelulares, tales como proliferación, angiogénesis, y movilidad celular. El receptor del factor de crecimiento derivado de plaquetas tiene una función importante en el mantenimiento, crecimiento y desarrollo de las células hematopoiéticas y no hematopoiéticas.

El PDGFR se expresa sobre las primeras células madre, mastocitos, células mieloides, células mesenquimales, y células de músculo liso. Solamente el PDGFR-ß está implicado en las leucemias mieloides - usualmente como un componente de translocalización con Tel, la proteína de interacción con Huntingtina (HIP1), o Rabaptina5. Las mutaciones de activación en el dominio de cinasa de PDGFR-α están asociadas con los tumores estromales gastrointestinales (GIST).

Ciertos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas proporcionadas en la presente son

inhibidores de las cinasas de tirosina receptoras PDGFR, y por consiguiente, estos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas son útiles para el tratamiento de las enfermedades y/o los trastornos que respondan a la inhibición de las cinasas de tirosina receptoras PDGFR. En ciertas modalidades, estos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas son útiles en el tratamiento de las células de cáncer hematopoiéticas y no hematopoiéticas. En ciertas modalidades, estos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas son útiles en el tratamiento de las enfermedades y/o los trastornos que incluyen, pero no se limitan a, leucemias mieloides y tumores estromales gastrointestinales (GIST).

Familia de receptores del factor de crecimiento endotelial vascular (VEGF)

VEGF, también conocido como cinasa de tirosina relacionada con fms-1 (FLT1), es una proteína de señalización importante involucrada tanto en la vasculogénesis (formación del sistema circulatorio embrionario) como en la angiogénesis (crecimiento de vasos sanguíneos a partir de la vasculatura previamente existente). Estructuralmente, el VEGF (factor de crecimiento endotelial vascular) pertenece a la familia de factores de crecimiento de citoquina-knot del PDGF (factor de crecimiento derivado de plaquetas). La sub-familia de factores de crecimiento del VEGF (factor de crecimiento endotelial vascular) incluye VEGF-A, VEGF-B, VEGF-C y VEGF-D. VEGF-A se enlaza con el receptor VEGFR-1 (Flt-1) y con el receptor

VEGFR-2 (KDR/Flk-1). VEGF-C y VEGF-D se enlazan con el receptor VEGFR-3 y median la linfangiogénesis. Los receptores VGFR median el proceso angiogénico, y por consiguiente, están involucrados en el soporte del progreso de cánceres y otras enfermedades que involucran una vascularización inapropiada (por ejemplo, retinopatía diabética, neovascularización coroidal debida a degeneración macular relacionada con la edad, soriasis, artritis, retinopatía de prematuridad, y hemangiomas infantiles).

Ciertos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas proporcionadas en la presente son inhibidores de las cinasas de tirosina receptoras VEGFR-2 (KDR), y por consiguiente, estos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas son útiles para el tratamiento de las enfermedades y/o los trastornos que respondan a la inhibición de las cinasas de tirosina receptoras VEGFR-2 (KDR). En ciertas modalidades, estos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas son útiles en el tratamiento de cáncer mediante la inhibición del desarrollo y/o progreso del cáncer.

Cinasa de tirosina tipo Fms

El ligando (FLT3L) de cinasa de tirosina tipo fms-3 (FLT3) es una de las citoquinas que afectan al desarrollo de múltiples linajes hematopoiéticos. Estos efectos se presentan a través del enlace de FLT3L con el receptor FLT3, también referido como cinasa de hígado fetal-2 (flk-2) y STK-1, una cinasa de tirosina receptora (RTK) expresada sobre las células totipotentes y progenitoras

213

hematopoiéticas. FLT3 es un miembro de la familia de cinasa de tirosina receptora tipo III (RTK). El ligando para FLT3 se expresa mediante las células estromales de médula y otras células, y se sinergiza con otros factores de crecimiento para estimular la proliferación de las células totipotentes, las células progenitoras, las células dendríticas, y las células aniquiladoras naturales. Flt3 tiene un papel importante en el mantenimiento, crecimiento y desarrollo de loas células hematopoiéticas y no hematopoiéticas.

El gen FLT3 codifica una RTK enlazada con membrana, que tiene un papel importante en la proliferación, diferenciación y apoptosis de las células durante la hematopoiesis normal. El gen FLT3 es principalmente expresado por las células progenitoras mieloides y linfoides tempranas. Los trastornos hematopoiéticos son trastornos pre-malignos, e incluyen, por ejemplo, los mielotrastornos proliferativos, tales como trombocitemia, trombocitosis esencial (ET), metaplasia mieloide angiogénica, mielofibrosis (MF), mielofibrosis con metaplasia mieloide (MMM), mielofibrosis idiopática crónica (IMF), y policitemia vera (PV), las citopenias, y los síndromes mielodisplásicos pre-malignos. Las malignidades hematológicas incluyen leucemias, linfomas (linfoma no de Hodgkin), enfermedad de Hodgkin (también denominada como linfoma de Hodgkin), y mieloma -- por ejemplo, leucemia linfocítica aguda (ALL), leucemia mieloide aguda (AML), leucemia promielocítica aguda (APL), leucemia linfocítica crónica (CLL), leucemia mieloide crónica (CML), leucemia neutrofílica crónica (CNL), leucemia no diferenciada aguda (AUL),

linfoma macrocelular anaplásico (ALCL), leucemia prolinfocítica (PML), leucemia mielomonocítica juvenil (JMML), leucemia linfocítica aguda de células-T de adultos, leucemia mieloide aguda con mielodisplasia de trilinaje (AML/TMDS), leucemia de linaje mixto (MLL), síndromes mielodisplásicos (MDSs), mielotrastornos proliferativos (MPD), mieloma múltiple, (MM), y sarcoma mieloide.

Se ha documentado la expresión aberrante del gen Flt3 en leucemias tanto de adultos como de la niñez, incluyendo leucemia mieloide aguda (AML), leucemia mieloide aguda con mielodisplasia de trilinaje (AML/TMDS), leucemia linfoblástica aguda (ALL), y síndrome mielodisplásico (MDS). Se han encontrado mutaciones activadoras del receptor Flt3 en aproximadamente el 35 por ciento de los pacientes con leucemia mieloblástica aguda (AML), y están asociadas con un pronóstico pobre. La mutación más común involucra la duplicación en el marco dentro del dominio yuxtamembrana, teniendo un del 5 al 10 por ciento adicional de pacientes una mutación puntual en la asparagina 835. Ambas mutaciones están asociadas con la activación constitutiva de la actividad de cinasa de tirosina de Flt3, y dan como resultado señales de proliferación y viabilidad en ausencia del ligando. Se ha demostrado que los pacientes que expresan la forma mutante del receptor, tienen una menor oportunidad de curarse. Por consiguiente, existe una evidencia acumulada de un papel para la actividad de cinasa Flt3 (mutada) híper-activada, en las leucemias humanas y en el síndrome mielodisplásico.

FLT-3 y c-Kit regulan el mantenimiento de las reservas de células totipotentes/progenitoras tempranas, así como el desarrollo de las células linfoides y mieloides maduras. Ambos receptores contienen un dominio de cinasa intrínseco que se activa sobre la dimerización mediada por ligando de los receptores. Después de que la activación, el dominio de cinasa induce la autofosforilación del receptor, así como la fosforilación de diferentes proteínas citoplásmicas que ayudan a propagar la señal de activación que conduce al crecimiento, diferenciación y sobrevivencia. Algunos de los reguladores corriente abajo de la señalización de los receptores FLT-3 y c-Kit incluyen PLCγ, cinasa-PI3, Grb-2, SHIP, y las cinasas relacionadas con Src. Se ha demostrado que ambas cinasas de tirosina receptoras tienen una función en una variedad de malignidades hematopoiéticas y no hematopoiéticas. Se han implicado las mutaciones que inducen la activación independiente del ligando de FLT-3 y c-Kit en leucemia mielógena aguda (AML), leucemia linfocítica aguda (ALL), mastocitosis y tumor estromal gastrointestinal (GIST). Estas mutaciones incluyen cambios de un solo aminoácido en el dominio de cinasa o duplicaciones internas en fila, mutaciones puntuales, o supresiones en el marco de la región yuxtamembrana de los receptores. En adición a las mutaciones activadoras, el estímulo (autocrino o paracrino) dependiente del ligando de FLT-3 o c-Kit de tipo silvestre sobre-expresadas, puede contribuir al fenotipo maligno.

Ciertos compuestos, composiciones farmacéuticas y

combinaciones farmacéuticas proporcionadas en la presente son inhibidores de las cinasas de tirosina receptoras FLT-3, y por consiguiente, estos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas son útiles para el tratamiento de las enfermedades y/o los trastornos que respondan a la inhibición de las cinasas de tirosina receptoras FLT-3. En ciertas modalidades, estos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas son útiles en el tratamiento de los trastornos hematopoiéticos. Los trastornos hematopoiéticos incluyen, pero no se limitan a, los trastornos mieloproliferativos, tales como trombocitemia, trombocitosis esencial (ET), metaplasia mieloide angiogénica, mielofibrosis (MF), mielofibrosis con metaplasia mieloide (MMM), mielofibrosis idiopática crónica (IMF), y policitemia vera (PV), las citopenias, y síndromes mielodisplásicos pre-malignos. Las malignidades hematológicas incluyen leucemias, linfomas (linfoma no de Hodgkin), enfermedad de Hodgkin (también denominada como linfoma de Hodgkin), y mieloma - por ejemplo, leucemia linfocítica aguda (ALL), leucemia mieloide aguda (AML), leucemia pro-mielocítica aguda (APL), leucemia linfocítica crónica (CLL), leucemia mieloide crónica (CML), leucemia neutrofílica crónica (CNL), leucemia no diferenciada aguda (AUL), linfoma macrocelular anaplásico (ALCL), leucemia pro-linfocítica (PML), leucemia mielomonocítica juvenil (JMML), leucemia linfocítica aguda de células-T de adultos, leucemia mieloide aguda con mielodisplasia de tri-linaje (AML/TMDS), leucemia de linaje mixto (MLL), síndromes

mielodisplásicos (MDSs), trastornos mieloproliferativos (MPD), mieloma múltiple, (MM), y sarcoma mieloide.

Receptor del Factor Estimulante de Colonias de Macrófagos (c-FMS)

El factor estimulante de colonias de macrófagos (M-CSF) es un miembro de la familia de proteínas referidas como factores estimulantes de colonias (CSFs). M-CSF es una citoquina secretada o una glicoproteína de superficie celular, comprendida de dos sub-unidades que se unen mediante un enlace de disulfuro, con una masa molecular total que varía de 40 a 90 kD. De una manera similar a otros CSFs, el M-CSF es producido por los macrófagos, los monocitos, y las células de tejido de las articulaciones humanas, tales como los condrocitos y los fibroblastos sinoviales, en respuesta a proteínas tales como interleucina-1 o factor de necrosis tumoral-α. M-CSF estimula la formación de las colonias de macrófagos a partir de las células madre progenitoras hematopoiéticas pluripotentes. Las células eucarióticas también producen M-CSF con el objeto de combatir la infección viral intercelular.

El M-CSF típicamente se enlaza a su receptor, c-FMS, con el objeto de ejercer un efecto biológico. c-FMS contiene cinco dominios Ig extracelulares, un dominio transmembrana, y un dominio intracelular con dos dominios de cinasa. Cuando el M-CSF se enlaza al c-FMS, el receptor se homo-dimeriza e inicia una cascada de sendas de transducción de señales, incluyendo las sendas de JAK/STAT, PI3K, y ERK.

El M-CSF es un regulador importante de la función, activación, y sobrevivencia de los monocitos/macrófagos. El M-CSF está involucrado en diferentes enfermedades, incluyendo artritis reumatoide (RA) y cáncer. Los macrófagos comprenden las células efectoras clave en la artritis reumatoide (RA). Se ha demostrado que el grado de infiltración sinovial de macrófagos en la artritis reumatoide (RA) se correlaciona estrechamente con el grado de destrucción de las articulaciones subyacentes. El M-CSF, endógenamente producido en la articulación reumatoide por los monocitos/macrófagos, fibroblastos, y células endoteliales, actúa sobre las células del linaje de los monocitos/macrófagos para promover su sobrevivencia y diferenciación hasta los osteoclastos destructores de hueso, y potencia las funciones pro-inflamatorias celulares, tales como citotoxicidad, producción de superóxido, fagocitosis, quimiotaxis, y producción de citoquina secundaria. Por ejemplo, el tratamiento con M-CSF en el modelo de artritis experimental inducida por sonicación de *Streptococcus agalactiae* de rata, conduce a una potenciación de la patología. De una manera similar, las inyecciones subcutáneas de M-CSF en el modelo de artritis inducida por colágeno de murino, el cual es un modelo para la artritis reumatoide (RA), da como resultado una exacerbación significativa de los síntomas de la enfermedad de artritis reumatoide (RA). Adicionalmente, los ratones MRL/lpr que son altamente susceptibles a la artritis reumatoide (RA) y a otras enfermedades autoinmunes, han elevado las concentraciones basales de M-CSF en

suero.

El enlace de M-CSF al c-FMS, y su subsiguiente activación de los monocitos/macrófagos es importante en un número de estados de enfermedad. En adición a la artritis reumatoide (RA) y al cáncer, los otros ejemplos de estados de enfermedad relacionados con M-CSF incluyen osteoporosis, artritis destructiva, aterogénesis, glomerulonefritis, enfermedad de Kawasaki, e infección por VIH-1, en donde tienen una función los monocitos/macrófagos y los tipos de células relacionados. Por ejemplo, los osteoclastos son similares a los macrófagos, y son regulados en parte por el M-CSF. Las señales de crecimiento y diferenciación inducidas por el M-CSF en las etapas iniciales de la maduración de los osteoclastos son esenciales para su subsiguiente actividad osteoclástica en el hueso. El M-CSF es esencial de manera única para la osteoclastogénesis.

El M-CSF tiene una función central en la aterogénesis, y en la hiperplasia proliferativa de la íntima después del trauma mecánico a la pared arterial. Se ha demostrado que todos los principales tipos de células en las lesiones ateroescleróticas expresan el M-CSF, y éste además se sobre-regula mediante su exposición a la lipoproteína oxidada.

La enfermedad de Kawasaki (KD) es una vasculitis pediátrica febril aguda de causa desconocida. Sus complicaciones más comunes y graves involucran la vasculatura coronaria en la forma de dilatación de aneurisma. Los niveles de M-CSF en suero se elevan de una manera significativa en la fase aguda de la enfermedad de

Kawasaki, y se normalizan en seguida del tratamiento con inmunoglobulina intravenosa. La artritis de células gigantes (GCA) es una vasculopatía inflamatoria que se presenta principalmente en los ancianos, en donde las células-T y los macrófagos se infiltran en las paredes de las arterias medianas y grandes, conduciendo a consecuencias clínicas que incluyen ceguera y embolia secundaria a oclusión arterial. La involucración activa de los macrófagos en la artritis de células gigantes (GCA) es evidenciada por la presencia de niveles elevados de los mediadores inflamatorios derivados de macrófagos dentro de las lesiones vasculares.

Se ha reportado que el M-CSF hace que los macrófagos derivados de monocitos humanos sean más susceptibles a la infección por VIH-1 *in vitro*. En un estudio reciente, el M-CSF aumentó la frecuencia con la cual se llegaban a infectar los macrófagos derivados de monocitos, la cantidad de ARNm de VIH expresado por célula infectada, y el nivel de ADN pro-viral expresado por cultivo infectado.

Ciertos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas proporcionadas en la presente son inhibidores de las cinasas de tirosina receptoras c-FMS, y por consiguiente, estos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas son útiles para el tratamiento de las enfermedades y/o los trastornos que respondan a la inhibición de las cinasas de tirosina receptoras c-FMS. En ciertas modalidades, estos compuestos, composiciones farmacéuticas y combinaciones

217

farmacéuticas son útiles en el tratamiento de enfermedades autoinmunes, enfermedades inflamatorias, y cáncer. En ciertas modalidades, estos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas son útiles en el tratamiento de las enfermedades y/o los trastornos que incluyen, pero no se limitan a, artritis reumatoide, cáncer de ovario, cáncer uterino, cáncer de mama, cáncer de próstata, cáncer de pulmón, cáncer de colon, cáncer de estómago, leucemia de células pilosas, dolor esquelético causado por metástasis tumoral u osteoartritis, dolor visceral, dolor inflamatorio, dolor neurogénico, osteoporosis, enfermedad de Paget, osteoartritis, falla de prótesis, sarcoma osteolítico, mieloma, metástasis tumoral ósea, lupus eritematoso sistémico, soriasis, síndrome de Sjogren, esclerosis múltiple, uveítis, ateroesclerosis, fibrosis, y vítreo-retinopatía proliferativa.

Receptor del factor de crecimiento tipo insulina 1 (IGF-1)

El receptor del factor de crecimiento tipo insulina 1 (IGF-1) es un receptor transmembrana que es activado por IGF-1, y por el factor de crecimiento relacionado IGF-2. IGF-1R media los efectos de IGF-1, el cual es una hormona de proteína de polipéptido similar en su estructura molecular a la insulina. IGF-1 tiene un papel importante en la sobrevivencia y proliferación en las células competentes en mitosis, y en el crecimiento (hipertrofia) en los tejidos, tales como músculo esquelético y músculo cardíaco. La senda de señalización de IGFR es de una importancia crítica durante el desarrollo normal del tejido de la glándula mamaria durante el embarazo y la lactancia.

Durante el embarazo, hay una intensa proliferación de las células epiteliales que forman el conducto y el tejido glandular. En seguida del destete, las células sufren apoptosis, y todo el tejido se destruye. Varios factores de crecimiento y hormonas están involucrados en este proceso global, y se cree que el IGF-1R tiene papeles en la diferenciación de las células, y un papel clave en la inhibición de la apoptosis hasta completar el destete.

El IGF-1R está implicado en varios cánceres, incluyendo, pero no limitándose a, cáncer de mama. En algunos casos, sus propiedades anti-apoptóticas permiten que las células cancerosas resistan a las propiedades citotóxicas de los fármacos quimioterapéuticos o la radioterapia. Además está implicado en el cáncer de mama, mediante el incremento del potencial metastásico del tumor original, al interferir con la capacidad para promover la vascularización.

Receptor c–Kit

Los compuestos de la presente invención también inhiben los procesos celulares que involucran al factor de células totipotentes (SCF, también conocido como el ligando de c-kit o el factor de Steel), tales como la inhibición de la autofosforilación del receptor de SCF (kit), y de la activación de la cinasa MAPK estimulada por SCF (cinasa de proteína activada por mitógeno). Las células MO7e son una línea celular de leucemia promegacariocítica humana, que depende de SCF para la proliferación.

c-Kit tiene una homología sustancial con el receptor de PDGF

(factor de crecimiento derivado de plaquetas), y con el receptor de CSF1 (c-Fms). Las investigaciones sobre diferentes líneas celulares eritroides y mieloides indican una expresión del gen c-Kit en la primeras etapas de la diferenciación. Ciertos tumores, tales como las células de glioblastoma, exhiben de la misma manera una expresión pronunciada del gen c-Kit.

Cinasa de linfoma anaplásico (Ki-1 o ALK)

La cinasa de linfoma anaplásico (ALK) es una cinasa de tirosina receptora de 200 kDa codificada por el gen *ALK* sobre el cromosoma 2p23. ALK fue primeramente identificada como parte de la proteína de fusión oncogénica NPM-ALK, en donde la porción N-terminal de la fosfoproteína nucleofosmina (NPM) se enlaza a la porción citoplásmica de ALK. Esta proteína de fusión oncogénica resulta a partir de la translocalización de (2;5)(p23;q35) que con frecuencia está asociada con el linfoma macrocelular anaplásico (ALCL). Esta translocalización produce un gen de fusión que codifica una proteína de transformación quimérica soluble que comprende la proteína de fusión oncogénica NPM-ALK. La porción NPM es responsable de la dimerización de la proteína de fusión, que conduce a la activación constitutiva de la cinasa, y a la oncogenicidad. ALK es altamente homóloga a la cinasa de tirosina de leucocitos, y pertenece a la súper-familia de receptores de insulina de las cinasas de tirosina receptoras. La ALK de longitud completa tiene la estructura típica de una RTK, con un dominio extracelular grande, un segmento transmembrana lipofílico, y un dominio de cinasa de

tirosina citoplásmica. Las proteínas de fusión de ALK mantienen la cola intracitoplásmica del receptor ALK en su término C. Esta región contiene un dominio catalítico, mientras que la región N-terminal de todas las proteínas de fusión tiene dominios de dimerización. Como una consecuencia de la dimerización, las quimeras de ALK sufren autofosforilación y llegan a ser constitutivamente activas.

El gen *ALK* codifica un receptor de cinasa de tirosina, cuya expresión fisiológica en mamíferos está limitada en gran parte a regiones específicas del sistema nervioso central y del sistema nervioso periférico. El gen *ALK* normal se expresa dominantemente en el sistema neural, y el ARNm de *ALK* se expresa esencialmente y transitoriamente en regiones específicas de los sistemas nerviosos central y periférico, tales como el tálamo, el cerebro medio, el bulbo olfatorio, y los ganglios periféricos, y se localiza principalmente en las células neuronales. ALK tiene una función importante en el desarrollo del cerebro y en el desarrollo y función normal del sistema nervioso al ejercer sus efectos sobre neuronas específicas del sistema nervioso.

También se ha detectado la expresión de la proteína de ALK en los tumores derivados a partir del sistema nervioso, tales como los neuroblastomas. a pleiotrofina (PTN) y la midquina, dos factores de crecimiento de enlace de heparina con actividades pleiotróficas involucrados en el desarrollo normal y en el crecimiento tumoral, pueden servir como posibles ligandos para ALK en mamíferos, aunque todavía no está claro si estas moléculas son ligandos

219

fisiológicos de ALK.

La cinasa de linfoma anaplásico (ALK) se ha implicado en la oncogénesis de los tumores hematopoiéticos y no hematopoiéticos. Se ha reportado la expresión aberrante de las proteínas del receptor ALK de longitud completa en un sub-conjunto de tumores no linfoides, incluyendo sarcomas, neuroblastomas, gliomas y glioblastomas, y las proteínas de fusión de ALK se han presentado en el linfoma macrocelular anaplásico (ALCL). Los linfomas macrocelulares anaplásicos (ALCLs) representan un sub-conjunto del linfoma no de Hodgkins, en donde el gen de cinasa de linfoma anaplásico (ALK) con frecuencia se fusiona con el gen de nucleofosmina (NPM), y se caracteriza por una morfología y expresión celular única de CD30. Se requiere de la actividad de ALK para la sobrevivencia de las células ALCL *in vitro* e *in vivo*. La actividad de cinasa ALK es esencial para un efecto anti-apoptótico, debido a las células que expresan NPM-ALK muertas en cinasa no se protegen contra la apoptosis inducida por doxorrubicina. ALK también está involucrada en diferentes translocalizaciones cromosómicas variantes, conduciendo todas a la expresión de las proteínas de fusión con una cinasa constitutivamente activa.

Las fosfolipasa C-γ, PI3K, STATs, y Src son objetivos corriente abajo importantes de NPM-ALK que contribuyen a sus actividades mitogénicas y anti-apoptóticas. Las quimeras de ALK activadas se enlazan a múltiples proteínas adaptadoras capaces de disparar diferentes sendas que regulan la proliferación, sobrevivencia, y

transformación celular. Los adaptadores conocidos incluyen Grb2, Shc, IRS-1, fosfolipasa Cγ (PLC-γ) PI3K, y JAK3, que activan numerosas moléculas corriente abajo, incluyendo ciclina D, ERK1/2, STAT, y AKT. La ablación genética de STAT3 en las células positivas para ALK conduce a la muerte celular, y previene la generación de neoplasmas de células-B. PLC-γ y AKT tienen una función esencial en la transformación mediada por ALK *in vitro*. Las sendas de Ras/ERK y PLC-γ pueden contribuir a la mejora del crecimiento celular, y Stat3 y PI3K/AKT pueden tener una función importante en la inhibición de apoptosis.

Homólogo de oncogén de virus de sarcoma V-ros UR2 1 (aviar), (gen ROS1)

La cinasa de tirosina transmembrana Ros, codificada para el proto-oncogén *c-ros*, es un receptor de cinasa de tirosina huérfano usualmente clasificado como un miembro de la sub-familia de receptores de insulina, y se expresa en el epitelio específico. El perfil de expresión temporal y en tejido de c-Ros en el pollo y en las ratas, sugiere que tiene una función en la diferenciación de las células epiteliales durante la embriogénesis, en particular en los túbulos de riñón y testículos. Se ha encontrado que el oncogén c-ros es constitutivamente activo en los glioblastomas.

También se ha demostrado el potencial oncogénico de la cinasa de tirosina Ros mediante la transformación de los fibroblastos NIH3T3 dependiente del ligando, los cuales se transfectaron establemente con un receptor quimérico consistente en el dominio

extracelular del receptor de TrkA/factor de crecimiento de nervios (NGF) y los dominios transmembrana y citoplásmicos de Ros. La función fisiológica de Ros se ha caracterizado en los ratones con una mutación dirigida de *c-ros*. Los ratones $Ros^{-/-}$ machos exhiben defectos en la diferenciación y regionalización del epitelio epididimal y, debido a este defecto, son estériles.

Cinasas de Serina/Treonina Receptoras (RTKs).

Cinasa Tipo Activina-4 (ALK-4) y Cinasa Tipo Activina-5 (ALK-5)

El Factor de Crecimiento Transformante-ß1 (TGF-ß1) es el miembro prototípico de una familia de citoquinas que incluye a los factores de crecimiento transformante-ß (TGF-ßs), activinas, inhibinas, proteínas morfogenéticas óseas, y sustancia inhibidora de Mullerian, que señalizan a través de una familia de receptores de cinasa de serina/treonina transmembrana individuales. Estos receptores se pueden dividir en dos clases, los receptores de cinasa tipo I o tipo activina, y los receptores tipo II. Los receptores de cinasa tipo activina se distinguen de los receptores tipo II en que los receptores de cinasa tipo activina (a) carecen de la cola intracelular rica en serina/treonina, (b) poseen dominios de cinasa de serina/treonina que son muy homólogos entre los receptores tipo I, y (c) comparten un motivo de secuencia común denominado como el dominio GS, el cual consiste en una región rica en residuos de glicina y seria. El dominio GS está en el extremo amino-terminal del dominio de cinasa intracelular, y es crítico para la activación por

parte del receptor tipo II. Varios estudios han demostrado que la señalización de TGF-ß requiere tanto de los receptores de cinasa tipo activina como de los receptores tipo II. De una manera específica, el receptor tipo II fosforila el dominio GS del receptor tipo I para TGF-ß, el receptor de cinasa tipo activina-5 (ALK5), en la presencia de TGF-ß. El ALK5, a su vez, fosforila las proteínas citoplásmicas smad 2 y smad3 en dos serinas carboxi-terminales. Las proteínas smad fosforiladas se translocalizan en el núcleo y activan los genes que contribuyen a la producción de matriz extracelular.

Las activinas transducen las señales de una manera similar a TGF-ß. Las activinas se enlazan a la cinasa de serina/treonina, al receptor de activina tipo II (ActRIIB), y el receptor tipo II activado híper-fosforila los residuos de serina/treonina en la región GS del receptor de cinasa tipo activina-4 (ALK4). La ALK4 activada, a su vez, fosforila Smad2 y Smad3. La formación consecuente de un complejo hetero-Smad da como resultado la regulación de la transcripción genética inducida por activina.

La activación del eje TGF-ß1 y la expansión de la matriz extracelular con contribuyentes tempranos y persistentes al desarrollo y progreso de la enfermedad renal crónica y de la enfermedad vascular. Además, TGF-ß1 tiene una función en la formación de la fibronectina y del inhibidor del activador de plasminógeno-1, que son los componentes de los depósitos escleróticos, a través de la acción de la fosforilación de smad3

mediante el receptor ALK5 de TGF-ß1.

La fibrosis progresiva en el riñón y en el sistema cardiovascular es una causa mayor de sufrimiento y muerte, y un contribuyente importante al costo del cuidado de la salud. TGF-ß1 se ha implicado en muchos trastornos fibróticos renales. TGF-ß1 se eleva en la glomerulonefritis aguda y crónica, nefropatía diabética, rechazo de aloinjerto, nefropatía por VIH, y nefropatía inducida por angiotensina. En estas enfermedades, los niveles de expresión de TGF-ß1 coinciden con la producción de matriz extracelular. Tres líneas de evidencia sugieren una relación causal entre TGF-ß1 y la producción de matriz. Primera, se puede inducir a los glomérulos normales, a las células mesangiales, y a las células no renales, para producir proteína de matriz extracelular e inhibir la actividad de proteasa mediante el TGF-ß1 exógeno *in vitro*. Segunda, los anticuerpos neutralizantes contra TGF-ß1 pueden impedir la acumulación de matriz extracelular en las ratas nefríticas. Tercera, los ratones transgénicos en TGF-ß1 o la transfección *in vivo* del gen de TGF-ß1 en riñones de rata normal, dieron como resultado el desarrollo rápido de glomeruloesclerosis. Por consiguiente, se indica la inhibición de la actividad de TGF-ß1 como una intervención terapéutica en la enfermedad renal crónica.

TGF-ß1 y sus receptores aumentan en los vasos sanguíneos lesionados, y se indican en la formación de neoíntima en seguida de angioplastía de globo.. En adición TGF-ß1 es un potente estimulante de la migración de células de músculo liso ("SMC") *in vitro,* y la

migración de las células de músculo liso (SMC) en la pared arterial es un factor contribuyente en la patogénesis de ateroesclerosis y restenosis. Más aún, en el análisis multivariado de los productos de las células endoteliales contra el colesterol total, el receptor ALK5 de TGF-ß se correlacionó con el colesterol total ($P < 0.001$). Adicionalmente, las células de músculo liso (SMC) derivadas a partir de lesiones ateroescleróticas humanas tienen un aumento de la proporción de los receptores ALK5 / TGF-ß tipo II. Debido a que TGF-ß1 se sobre-expresa en las lesiones vasculares fibro-proliferativas, se debería permitir a las células variantes del receptor-I crecer en una forma lenta pero incontrolada, mientras que se sobre-producen los componentes de matriz extracelular. TGF-ß1 se inmunolocaliza en los macrófagos no espumosos de las lesiones ateroescleróticas en donde ocurre la síntesis activa de la matriz, sugiriendo que los macrófagos no espumosos pueden participar en la modulación de la expresión del gen de matriz en la remodelación ateroesclerótica por medio de un mecanismo dependiente de TGF-ß. Por consiguiente, también se indica la inhibición de la acción de TGF-ß1 sobre ALK5 en ateroesclerosis y restenosis.

La fibrosis hepática es el resultado de la respuesta desbalanceada de sanado de heridas a la lesión hepática crónica desencadenada por un número de agentes, tales como los virus de hepatitis B y de hepatitis C, alcohol o fármacos, y enfermedades autoinmunes. Por último, la fibrosis hepática podría conducir a cirrosis amenazante de la vida y a cáncer de hígado. Se sabe que

varias sendas de señalización celular se alteran después de la lesión hepática crónica.

Está bien documentado que la señalización de TGFß, sus receptores y proteínas de señalización de Smad asociadas, están presentes en los tipos de células involucradas en la fibrogénesis. Se ha encontrado que los niveles circulantes de TGFß se elevan en un número de modelos animales de enfermedades fibróticas, incluyendo fibrosis hepática. Los ratones transgénicos con sobre-expresión de TGFß1 desarrollan fibrosis en múltiples órganos, incluyendo hígado, riñón, pulmones y corazón. La señalización elevada de TGFß está involucrada en todos los tipos de enfermedades fibróticas, incluyendo fibrosis hepática. TGFß media su señal mediante el enlace con dos receptores de cinasa de serina/treonina, TGFßRII y ALK5. La expresión de un TGFßRII negativo dominante mostró efectos benéficos en un modelo de fibrosis hepática de rata inducida por dimetil-nitrosamina. La inhibición de la expresión de TGFß utilizando un planteamiento anti-sentido también redujo la fibrosis hepática inducida por el ligamiento del conducto biliar. Por consiguiente, la inhibición de la señalización de TGFß podría ser un tratamiento efectivo para las enfermedades fibróticas del hígado.

TGF-ß1 también se indica en la reparación de heridas. Se han utilizado anticuerpos neutralizantes para TGF-ß1 en un número de modelos para ilustrar que la inhibición de la señalización de TGF-ß1 es benéfica para restablecer la función después de la lesión, mediante la limitación de la formación excesiva de escara durante el

proceso de sanado. Por ejemplo, los anticuerpos neutralizantes para TGF-ß1 y TGF-ß2 redujeron la formación de escara, y mejoraron la citoarquitectura de la neodermis mediante la reducción del número de monocitos y macrófagos, así como mediante la disminución de la fibronectina dérmica y del depósito de colágeno en ratas. Más aún, los anticuerpos de TGF-ß también mejoran el sanado de las heridas de córnea en los conejos, y aceleran el sanado de las heridas de las úlceras gástricas en la rata. Por consiguiente, la limitación de la actividad de TGF-ß sería benéfica en muchos tejidos, y cualquier enfermedad con elevación crónica del TGF-ß se beneficiaría con la inhibición de las sendas de señalización de smad2 y smad3. El TGF-ß también está implicado en las adhesiones peritoneales. Por consiguiente, los inhibidores de ALK5 serían benéficos para prevenir las adhesiones fibróticas peritoneales y sub-dérmicas en seguida de los procedimientos quirúrgicos. El TGF-ß también está implicado en el fotoenvejecimiento de la piel.

La señalización de TGF-ß también está implicada en el desarrollo de los trastornos pulmonares, en particular hipertensión pulmonar y fibrosis pulmonar. Los niveles de TGF-ß1 aumentan en los modelos animales de hipertensión pulmonar. Otros estudios han sugerido que el TGF-ß1 derivado de las células endoteliales pulmonares puede estimular el crecimiento de las células de músculo liso vascular pulmonar, las cuales pueden ser subyacentes a la mejor muscularización observada en la vasculatura pulmonar de los individuos con hipertensión pulmonar. La apoptosis de las células

endoteliales microvasculares pulmonares estimula el crecimiento de las células de músculo liso vascular. Por consiguiente, se indica la inhibición de la acción de TGF-ß1 sobre ALK5 como una intervención terapéutica en la hipertensión pulmonar.

Adicionalmente, la señalización de TGF-ß regulada por dys también se ha implicado en el desarrollo de fibrosis pulmonar idiopática. La activación de ALK5 da como resultado la activación de Smad3 y la modulación corriente abajo de la expresión de los genes involucrados en el proceso fibrótico, tales como inhibidor del activador de plasminógeno-1, pro-colágeno 3A1, y factor de crecimiento del tejido conectivo. Se ha demostrado que los niveles de TGF-ß1 y sus mediadores pro-fibróticos corriente abajo se sobre-regulan en el lavado broncoalveolar tomado a partir de los pacientes con fibrosis pulmonar idiopática y en los modelos animales de fibrosis pulmonar idiopática. La sobre-expresión transitoria del TGF-ß1 activo en los pulmones de murino, utilizando transferencia genética mediada por el vector adenoviral, dio como resultado la fibrosis pulmonar progresiva en los ratones de tipo silvestre, mientras que no se vio fibrosis alguna en los pulmones de los ratones con eliminación genética de Smad3 hasta 28 días en seguida del estímulo con TGF-ß1. Por consiguiente, la inhibición de la activación de ALK5 mediante TGF-ß1 también se indica para la fibrosis pulmonar.

La señalización de activina y la sobre-expresión de activina están relacionadas con los trastornos patológicos que involucran

acumulación de matriz extracelular y fibrosis, respuestas inflamatorias, caquexia o consunción, enfermedades o respuestas patológicas en el sistema nervioso central, e hipertensión. Los estudios han demostrado que el TGF-ß y la activina pueden actuar de una manera sinérgica para inducir la producción de matriz extracelular. La señalización de activina también está implicada en el desarrollo de los trastornos pulmonares, en particular hipertensión pulmonar y fibrosis pulmonar. Por ejemplo, la expresión de activina A en las muestras de pulmón a partir de los pacientes con fibrosis pulmonar intersticial demostró una fuerte expresión de activina A en el epitelio metaplásico, en las células de músculo liso hiperplásicas, en las células descamadas, y en los macrófagos alveolares. Las arterias pulmonares a partir de los pacientes con hipertensión pulmonar primaria o secundaria mostraron abundante activina A inmuno-reactiva en las células de músculo liso. Estos hallazgos sugieren una función potencial para este factor de crecimiento, la activina A, en la patogénesis de la remodelación del tejido pulmonar asociada con fibrosis pulmonar intersticial e hipertensión pulmonar. Un aumento en los fibroblastos y en el tejido conectivo asociado es una característica de la fibrosis pulmonar y de la hipertensión pulmonar. Se ha demostrado que la activina A modula la actividad de los fibroblastos pulmonares humanos (HFL1), en particular con respecto a l proliferación y su diferenciación en miofibroblastos, y por consiguiente, la activina A tiene efectos potenciales sobre la proliferación de los fibroblastos pulmonares y su diferenciación en

miofibroblastos, y puede contribuir a la remodelación estructural observada en la fibrosis pulmonar y en la hipertensión. La inducción de fibrosis pulmonar mediada por el estímulo con bleomicina en ratas da como resultado la expresión sobre-regulada de la activina A en los macrófagos infiltrados en el pulmón, y se detectó en los fibroblastos acumulados en el área fibrótica. La administración de folistatina, un antagonista de la señalización de activina, a las ratas tratadas con bleomicina, redujo de una manera significativa el número de macrófagos y neutrófilos en el lavado broncoalveolar, y redujo el contenido de proteína. La folistatina redujo notoriamente el número de células de infiltración, mitigó la destrucción de la arquitectura pulmonar, y atenuó la fibrosis pulmonar.

La reducción en la señalización de TGF-ß, a través de su efector Smad3, mejora las propiedades mecánicas y la concentración mineral de la matriz ósea, así como la masa ósea, haciendo posible que el hueso resista mejor las fracturas. Por consiguiente, también se indica la inhibición de la activación de ALK5 mediante TGF-ß1 para aumentar la concentración de la densidad mineral y el contenido de hueso, y se puede utilizar para tratar una amplia variedad de trastornos óseos, los cuales incluyen, pero no se limitan a, osteopenia, osteoporosis, fracturas, y otros trastornos en donde una baja densidad mineral ósea sea un signo de la enfermedad.

La osteoporosis es un trastorno esquelético sistémico caracterizado por una baja masa ósea y un deterioro micro-arquitectónico del tejido óseo, con un aumento consecuente en la

fragilidad del hueso y susceptibilidad a las fracturas. El síndrome osteoporótico tiene múltiples facetas, que abarcan trastornos primarios, tales como la osteoporosis post-menopáusica o relacionada con la edad, y las condiciones secundarias que acompañan a los estados de enfermedad o a los medicamentos. Las propiedades mecánicas y la composición de la matriz ósea, junto con la masa ósea y la arquitectura, son determinantes críticos de la capacidad del hueso para resistir a las fracturas. Por consiguiente, en ciertas modalidades, los compuestos, composiciones farmacéuticas y combinaciones farmacéuticas proporcionadas en la presente, se utilizan para prevenir o tratar las condiciones óseas que estén asociadas con un aumento en el agotamiento o en la resorción de calcio, o en donde sea deseable la estimulación de la formación de hueso y la fijación de calcio en el hueso.

Las enfermedades o condiciones mediadas por la inhibición de ALK-5 o por la inhibición de ALK-4 incluyen, pero no se limitan a, glomerulonefritis, nefropatía diabética, nefritis por lupus, nefropatía inducida por hipertensión, fibrosis intersticial renal, fibrosis renal resultante de complicaciones de exposición a fármacos, nefropatía asociada con VIH, necropatía de trasplante, fibrosis hepática debida a todas las etiologías, disfunción hepática atribuible a infecciones, hepatitis inducida por alcohol, trastornos del árbol biliar, fibrosis pulmonar, hipertensión pulmonar, lesión pulmonar aguda, síndrome de insuficiencia respiratoria de adultos, fibrosis pulmonar idiopática, enfermedad pulmonar obstructiva crónica, enfermedad pulmonar

debida a agentes infecciosos o tóxicos, fibrosis cardíaca posterior a infarto, insuficiencia cardíaca congestiva, cardiomiopatía dilatada, miocarditis, estenosis vascular, restenosis, ateroesclerosis, escarificación ocular, escarificación de córnea, vítreo-retinopatía proliferativa, formación excesiva o hipertrófica de escara o queloide en la dermis que se presente durante sanado de heridas resultantes de trauma o de heridas quirúrgicas, adhesión peritoneal y subdérmica, esclerodermia, fibroesclerosis, esclerosis sistémica progresiva, dermatomiositis, polimiositis, artritis, úlceras, función neurológica deteriorada, disfunción eréctil masculina, enfermedad de Alzheimer, síndrome de Raynaud, cánceres fibróticos, crecimiento de metástasis tumoral, fibrosis inducida por radiación, trombosis, y condiciones óseas tales como osteopenia y osteoporosis, las cuales estén asociadas con un aumento en el agotamiento o en la resorción de calcio, o en donde sea deseable la estimulación de la formación de hueso y la fijación de calcio en el hueso.

Las enfermedades o condiciones mediadas por la inhibición de ALK-5 incluyen en particular, pero no se limitan a, enfermedad renal crónica, enfermedad renal aguda, sanado de heridas, artritis, osteoporosis, enfermedad del riñón, insuficiencia cardíaca congestiva, enfermedades inflamatorias u obstructivas de las vías respiratorias, hipertensión pulmonar, úlceras (incluyendo úlceras diabéticas, úlceras crónicas, úlceras gástricas, y úlceras duodenales), trastornos oculares, heridas de córnea, nefropatía diabética, función neurológica deteriorada, enfermedad de Alzheimer,

ateroesclerosis, adhesión peritoneal y sub-dérmica, cualquier enfermedad en donde la fibrosis sea un componente mayor, incluyendo, pero no limitándose a, fibrosis del riñón, fibrosis pulmonar, y fibrosis hepática, por ejemplo, virus de hepatitis B (HBV), virus de hepatitis C (HCV), hepatitis inducida por alcohol, hemocromatosis, cirrosis biliar primaria, restenosis, fibrosis retroperitoneal, fibrosis mesentérica, endometriosis, queloides, cáncer, función ósea anormal, trastornos inflamatorios, escaración y fotoenvejecimiento de la piel.

Ciertos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas proporcionadas en la presente son inhibidores de los receptores de ALK-4, y por consiguiente, estos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas son útiles para el tratamiento de las enfermedades y/o los trastornos presentados en la presente, que sean mediados por los receptores de ALK-4. Ciertos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas proporcionadas en la presente son inhibidores de los receptores de ALK-5, y por consiguiente, estos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas son útiles para el tratamiento de las enfermedades y/o los trastornos presentados en la presente, que sean mediadas por los receptores de ALK-5. Ciertos compuestos, composiciones farmacéuticas y combinaciones farmacéuticas proporcionadas en la presente son inhibidores de los receptores de ALK-4 y de los receptores de ALK-5, y por consiguiente, estos

compuestos, composiciones farmacéuticas y combinaciones farmacéuticas son útiles para el tratamiento de las enfermedades y/o los trastornos presentados en la presente, que sean mediados por los receptores de ALK-4 y por los receptores de ALK-5.

En ciertas modalidades, los compuestos, composiciones farmacéuticas y combinaciones farmacéuticas proporcionadas en la presente, se utilizan para tratar y/o prevenir las enfermedades inflamatorias u obstructivas de las vías respiratorias, incluyendo, pero no limitándose a, asma (tanto asma intrínseco (no alérgico) como asma extrínseco (alérgico)), síndrome de insuficiencia respiratoria de adultos/aguda (ARDS), enfermedad obstructiva crónica pulmonar o de las vías respiratorias (COPD o COAD), incluyendo bronquitis crónica o disnea asociada con la misma, bronquitis aguda, bronquitis araquídica, bronquitis catarral, bronquitis cruposa, bronquitis ftinoide, enfisema, neumoconiosis (una enfermedad inflamatoria, comúnmente ocupacional, de los pulmones, con frecuencia acompañada por obstrucción de las vías respiratorias, ya sea crónica o aguda, y ocasionada por la inhalación repetida de polvos) de cualquier tipo o génesis, incluyendo, por ejemplo, aluminosis, antracosis, asbestosis, calicosis, ptilosis, siderosis, silicosis, tabacosis y bisinosis, así como exacerbación de la hiper-reactividad de las vías respiratorias a consecuencia de otra terapia con fármacos, en particular otra terapia con fármacos inhalados.

La eficacia profiláctica en el tratamiento de asma es evidenciada por una frecuencia o gravedad reducida del ataque

sintomático, por ejemplo, del ataque asmático agudo o broncoconstrictor, mejora en la función pulmonar, o mejor hiper-reactividad de las vías respiratorias. Otra evidencia es un requerimiento reducido de otra terapia sintomática, es decir, terapia para, o pretendida para, restringir o abortar el ataque sintomático cuando se presente, por ejemplo anti-inflamatoria (por ejemplo, corticosteroides) o broncodilatadora. El beneficio profiláctico en asma puede ser evidente en particular en los sujetos susceptibles al "ahogamiento matutino". El "ahogamiento matutino" es un síndrome asmático reconocido, común a un porcentaje sustancial de asmáticos, y caracterizado por ataque de asma, por ejemplo, entre las horas de aproximadamente 4 a 6 am, es decir, en un tiempo normalmente distante sustancialmente de cualquier terapia sintomática de asma previamente administrada.

En ciertas modalidades, los compuestos, composiciones farmacéuticas y combinaciones farmacéuticas proporcionadas en la presente, se utilizan para tratar y/o prevenir hipertensión pulmonar, incluyendo, pero no limitándose a, hipertensión pulmonar primaria (PPH); hipertensión pulmonar secundaria (SPH); hipertensión pulmonar primaria familiar; hipertensión pulmonar primaria esporádica; hipertensión pulmonar pre-capilar; hipertensión arterial pulmonar (PAH); hipertensión de arteria pulmonar; hipertensión pulmonar idiopática; arteriopatía pulmonar trombótica (TPA); arteriopatía pulmonar plexogénica; arteriopatía pulmonar funcional clases I a IV; e hipertensión pulmonar asociada con, relacionada

con, o secundaria a, disfunción de ventrículo izquierdo, enfermedad de válvula mitral, pericarditis constrictiva, estenosis aórtica, cardiomiopatía, fibrosis mediastinal, drenaje venoso pulmonar anómalo, enfermedad oclusiva venosa pulmonar, enfermedad vascular de colágeno, enfermedad cardíaca congénita, infección por virus VIH, fármacos y toxinas, tales como fenfluraminas, enfermedad cardíaca congénita, hipertensión venosa pulmonar, enfermedad pulmonar obstructiva crónica, enfermedad intersticial pulmonar, respiración trastornada en el sueño, trastorno de hipoventilación alveolar, exposición crónica a alta altitud, enfermedad pulmonar neonatal, displasia capilar alveolar, enfermedad drepanocítica, otro trastorno de la coagulación, tromboémbolos crónicos, enfermedad del tejido conectivo, lupus, esquistosomiasis, sarcoidosis, o hemangiomatosis capilar pulmonar.

En ciertas modalidades, la hipertensión pulmonar tratada con los compuestos, composiciones farmacéuticas y combinaciones farmacéuticas proporcionadas en la presente, es hipertensión pulmonar asociada con trastornos del sistema respiratorio y/o hipoxemia, incluyendo enfermedad pulmonar obstructiva crónica, enfermedad intersticial pulmonar, respiración trastornada en el sueño, trastornos de hipoventilación alveolar, exposición crónica a alta altitud, enfermedad pulmonar neonatal, y displasia capilar alveolar, pero en especial enfermedad pulmonar obstructiva crónica.

En ciertas modalidades, los compuestos, composiciones farmacéuticas y combinaciones farmacéuticas proporcionadas en la

presente, se utilizan para tratar las enfermedades o los trastornos mediados por la inhibición de ALK-5 o por la inhibición de ALK-4, incluyendo, pero no limitándose a, hipertensión pulmonar, fibrosis pulmonar, fibrosis hepática, u osteoporosis. En ciertas modalidades, los compuestos, composiciones farmacéuticas y combinaciones farmacéuticas proporcionadas en la presente, se utilizan para tratar fibrosis pulmonar, incluyendo, pero no limitándose a, fibrosis pulmonar idiopática.

La miostatina, un miembro de la familia del factor de crecimiento transformante ß (TGFß), es un regulador negativo clave de la masa músculo-esquelética. En el ganado de doble músculo y en un cuerpo humano con hipertrofia músculo-esquelética, se detectaron diferentes mutaciones en el gen de miostatina. Se confirmó la importante función de la miostatina para el crecimiento y los trastornos músculo-esqueléticos en una amplia variedad de estudios *in vivo* e *in vitro*. Por ejemplo, la sobre-expresión de miostatina específica del músculo en los ratones provoca una pérdida de masa muscular, mientras que los ratones nulos en miostatina tienen una masa músculo-esquelética incrementada y grasa corporal reducida. De conformidad con lo anterior, la administración sistémica de miostatina induce caquexia, mientras que la inhibición de miostatina, por ejemplo, mediante el anticuerpo neutralizante de miostatina JA16, aumenta la masa y fuerza muscular en los ratones mdx de tipo silvestre y distróficos. En adición, se han observado niveles elevados de miostatina en las atrofias musculares

tanto experimentales como clínicas, tal como en los pacientes con el virus de inmunodeficiencia humana (VIH), cáncer, o cirrosis hepática, así como en la sarcopenia de la ancianidad, y bajo tratamiento con glucocorticoides. Estos hallazgos muestran el alto potencial de los inhibidores de miostatina como tratamientos para las atrofias y distrofias musculares.

La miostatina señaliza a través de Smad2/3, más aún, se ha demostrado que la miostatina madura actúa por medio de la de activina tipo IIb y los receptores de cinasa tipo receptor de activina en los adipocitos. Se cree que la miostatina inhibe la diferenciación y provoca atrofia por medio de la señalización del receptor de cinasa tipo receptor de activina. Más aún, la inhibición de la señalización del receptor de cinasa tipo receptor de activina promueve la diferenciación de las skMC y provoca la hipertrofia de las skMC.

Los compuestos, composiciones farmacéuticas y combinaciones farmacéuticas proporcionadas en la presente también se utilizan para tratar enfermedades musculares, incluyendo atrofias musculares (por ejemplo, desuso), distrofias musculares (por ejemplo, distrofia muscular de Duchenne, distrofia muscular de Becker, distrofia muscular de la cintura escapulohumeral o pélvica, distrofia facioescapulohumeral), sarcopenia, y caquexia.

Familia de la Cinasa Aurora

Las cinasas Aurora son cinasas de proteína serina/treonina que regulan muchos procesos durante la división celular, y son esenciales para la proliferación celular. Las cinasas Aurora tienen

una función esencial en la orquestación de la separación del cromosoma y la citoquinesis durante la mitosis. La ploidez correcta de las células requiere de una separación mitótica precisa del cromosoma. La cinasa Aurora controla la segregación de cromatida y ayuda a la célula en división a compartir sus materiales genéticos con sus células hijas. Los defectos en esta segregación puede provocar inestabilidad genética, una condición que está altamente asociada con la tumorigénesis. Además de estar implicados como reguladores mitóticos, estos tres miembros de la familia de mamífero han generado un interés significativo en el campo de la investigación del cáncer, debido a sus perfiles de expresión elevados en muchos cánceres humanos.

Se han identificado tres cinasas Aurora en las células de mamífero: Cinasa Aurora A; Cinasa Aurora B; y Cinasa Aurora C (Aie1). Las cinasas Aurora humanas presentan una organización de dominio similar, con un dominio N-terminal de 39 a 129 residuos de longitud, una cinasa de dominio de proteína, y un dominio C-terminal corto que contiene de 15 a 20 residuos. Todas tienen un dominio de cinasa altamente conservado, pero difieren en sus regiones N-terminales, las cuales varían en longitud y comparten una baja conservación de la secuencia, lo cual determina su selectividad durante las interacciones de proteína-proteína. Las cinasas Aurora tienen un sitio de enlace de ATP con una hendidura adyacente que no está presente en otras cinasas.

La familia de Aurora A (también conocida como Aurora 2, AIK,

BTAK e IAK1) funciona durante la pro-fase de la mitosis, y se requiere para la función correcta de los centrosomas (los centros organizadores de microtúbulos en las células eucarióticas). La cinasa Aurora A funciona en la separación del centrosoma y se localiza en los centrosomas, en los polos de huso, y en los microtúbulos de huso, en la pro-fase hasta la telofase. Los niveles de proteína y la actividad de cinasa de la cinasa Aurora aumentan ambos en la fase tardía G_2-M. La cinasa Aurora A es oncogénica y con frecuencia se sobre-expresa/se activa en muchas líneas celulares y tejidos de cáncer humano, incluyendo los cánceres humanos de ovario y e mama.

La Aurora B (también conocida como Aurora 1, AIK2, ARK2, y AIM-1) es regulada por el ciclo celular, y tiene una función en los eventos que se presentan durante la anafase y/o la telofase. La Aurora B funciona en la unión del huso mitótico al centrómero. La cinasa Aurora B es una proteína pasajera cromosómica que se localiza primero en los centrómeros, y luego en la zona media de las células mitóticas durante la telofase. La fosforilación de la histona H3 es importante para la condensación del cromosoma y la entrada en la mitosis. La fosforilación de la histona H3 es controlada por Aurora A y Aurora B.

La Aurora C (Aie1 de ratón y AIE2 humana, también conocida como STK-13, y AIK3 AURKC) exhibe un patrón de expresión específico de los testículos. La cinasa Aurora C, como la cinasa Aurora B, puede funcionar como una proteína pasajera cromosómica

que se localiza primero en los centrómeros y luego en la zona media de las células mitóticas. La Aurora C fue primeramente detectada en los racimos de los cromocentros de los espermatocitos de diploteno, y se concentró en los centrómeros en las metafases I y II. Es interesante que la Aurora C también se encontró a lo largo de los ejes de los cromosomas, incluyendo tanto las regiones de los centrómeros como los brazos de los cromosomas en la diacinesis. Durante las transiciones de la anafase I / telofase I y de la anafase II / telofase II, la Aurora C se relocalizó en la zona media del huso y en el cuerpo medio. El nivel de transcripción de la Aurora C se eleva en varios tipos de células de cáncer humanas.

Cinasas de Tirosina No Receptoras

Las cinasas de tirosina no receptoras representan una colección de enzimas celulares que carecen de secuencias extracelulares y transmembrana. Se han identificado más de veinticuatro cinasas de tirosina no receptoras individuales, las cuales comprenden once (11) sub-familias (Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack, y LIMK). La sub-familia de cinasas de tirosina no receptoras Src está comprendida del número más grande de PTKs, e incluye Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, e Yrk. La sub-familia de enzimas Src se ha relacionado con la oncogénesis y con las respuestas inmunitarias.

La familia de cinasas Src está implicada en cáncer, disfunción del sistema inmune, osteopetrosis, y enfermedades de remodelación ósea, y, por consiguiente, las cinasas Src se consideran como

objetivos terapéuticos potenciales para diferentes enfermedades humanas. La expresión de Src está relacionada con cánceres, tales como cáncer de colon, de mama, hepático, y pancreático, con ciertas leucemias de células-B, y con los linfomas. En adición, la Src anti-sentido expresada en células tumorales de ovario y de colon inhibe el crecimiento tumoral.

Csk, o la cinasa Src C-terminal, fosforila y, por lo mismo, inhibe la actividad catalítica de Src. Se ha logrado la supresión de la destrucción ósea artrítica mediante la sobre-expresión de Csk en los sinoviocitos y osteoclastos reumatoides. Esto implica que la inhibición de Src puede prevenir la destrucción de las articulaciones que es característica en los pacientes que sufren de artritis reumatoide. La Src también tiene una función en la réplica del virus de hepatitis B. El factor de transcripción viralmente codificado HBx activa la Src en un paso requerido para la propagación del virus.

Otras cinasas de la familia Src también son objetivos terapéuticos potenciales. La Lck tiene una función en la señalización de las células-T, y los ratones que carecen del gen Lck tienen una mala capacidad para desarrollar timocitos. La función de Lck como un activador positivo de la señalización de células-T sugiere que los inhibidores de Lck pueden ser útiles para el tratamiento de una enfermedad autoinmune, tal como artritis reumatoide. Hck, Fgr, y Lyn son mediadores importantes de la señalización de integrina en los leucocitos mieloides. La inhibición de estos mediadores de cinasa, por consiguiente, puede ser útil para el tratamiento de inflamación.

Familia de Cinasa Janus (JAK)

La cinasa Janus (JAK) es una familia de cinasas de tirosina no receptoras intracelulares, de un tamaño en el intervalo de 120 a 140 kDa, que transducen las señales mediadas por citoquina por medio de la senda de JAK-STAT. La familia JAK incluye cuatro miembros: JAK1, JAK2, JAK3 y TYK2. Las familias de receptores de citoquina Tipo I y Tipo II no poseen actividad catalítica de cinasa y, por consiguiente, se apoyan en la familia de cinasas de tirosina JAK para fosforilar y activar las proteínas corriente abajo involucradas en sus sendas de transducción de señales.

Los receptores existen como polipéptidos emparejados, exhibiendo, por consiguiente, dos dominios de transducción de señales intracelulares. Las JAKs poseen dos dominios de transferencia de fosfato casi idénticos, exhibiendo un dominio la actividad de cinasa, mientras que el otro tiene una función en la señalización corriente abajo. Las JAKs se asocian con una región rica en prolina en cada dominio intracelular que está adyacente a la membrana celular y se denomina como una región de cuadro1/ cuadro2. Después de que el receptor se asocia con su citoquina/ ligando respectivo, pasa a través de un cambio de conformación, poniendo las dos JAKs suficientemente cerca para fosforilarse una a la otra. La autofosforilación de JAK induce un cambio de conformación dentro de sí mismo, haciéndole posible transducir la señal intracelular mediante la fosforilación y activación adicional de los factores de transcripción denominados como STATs. Los STATs

231

activados se disocian del receptor y forman dímeros antes de translocalizarse en el núcleo celular, en donde regulan la transcripción de los genes seleccionados.

JAK1 es esencial para señalizar ciertas citoquinas Tipo I y Tipo II. Interactúa con la cadena gamma común (γc) de los receptores de citoquina tipo I, para provocar las señales a partir de la familia de receptores de IL-2 (por ejemplo, IL-2R, IL-7R, IL-9R e IL-15R), la familia de receptores de IL-4 (por ejemplo, IL-4R e IL-13R), la familia de receptores de gp130 (por ejemplo, IL-6R, IL-11R, LIF-R, OSM-R, el receptor de cardiotrofina-1 (CT-1R), el receptor del factor neurotrófico ciliar (CNTF-R), el receptor de neurotrofina-1 (NNT-1R), y Leptina-R). JAK1 también es importante para transducir una señal mediante los interferones tipo I (IFN-α/ß) y tipo II (IFN-γ), y los miembros de la familia IL-10 por medio de los receptores de citoquina tipo II. JAK1 tiene una función crítica en el inicio de las respuestas a múltiples familias de receptores de citoquina mayores.

JAK2 se ha implicado en la señalización por parte de los miembros de la familia de receptores de citoquina tipo II (por ejemplo, los receptores de interferones), la familia de receptores de GM-CSF (IL-3R, IL-5R y GM-CSF-R), la familia de receptores de gp130 (por ejemplo, IL-6R), y los receptores de una sola cadena (por ejemplo, Epo-R, Tpo-R, GH-R, PRL-R). La señalización de JAK2 se activa corriente abajo desde el receptor de prolactina. Se han encontrado fusiones del gen JAK2 con los genes TEL(ETV6) (TEL-JAK2) y PCM1 en los pacientes de leucemia. Además, se han

implicado mutaciones en JAK2 en policitemia vera, trombocitemia esencial, y en otros trastornos mieloproliferativos. Esta mutación, un cambio de valina a fenilalanina en la posición 617, parece hacer que las células hematopoiéticas sean más sensibles a los factores de crecimiento tales como eritropoietina y trombopoietina.

JAK3 funciona en la transducción de señales e interactúa con los miembros de la familia STAT (transducción de señales y activadores de transcripción). JAK3 se expresa predominantemente en las células inmunes y transduce una señal en respuesta a su activación por medio de la fosforilación de tirosina mediante los receptores de interleucina. Las mutaciones que abrogan la función de JAK3 provocan una SCID (enfermedad de inmunodeficiencia combinada grave) autosomal. La expresión de JAK3 está restringida en su mayor parte a las células hematopoiéticas. Se expresa más comúnmente en las células-T y en las células aniquiladoras naturales (NK), pero se ha inducido en otros leucocitos, incluyendo los monocitos. JAK3 está involucrada en la transducción de señales mediante los receptores que emplean la cadena gamma común (γC) de la familia de receptores de citoquina tipo I (por ejemplo, IL-2R, IL-4R, IL-7R, IL-9R, IL-15R, e IL-21R) [2]. Las mutaciones de JAK3 dan como resultado una inmunodeficiencia combinada grave (SCID).

La cinasa de tirosina 2 (TYK2) está implicada en la señalización de IFN-α, IL-6, IL-10 e IL-12.

Cinasa de Proteína Tirosina Específica de Leucocitos (Lck)

La Lck (o la cinasa de proteína tirosina específica de

leucocitos) es una proteína localizada en los linfocitos. La Lck es un miembro de la familia de cinasas de tirosina Src, y fosforila los residuos de tirosina de ciertas proteínas involucradas en las sendas de señalización intracelular de los linfocitos.

La Lck se encuentra más comúnmente en las células-T. Se asocia con las colas citoplásmicas de los co-receptores de CD4 y CD8 sobre las células auxiliares-T y las células-T citotóxicas, respectivamente, para ayudar en la señalización a partir del complejo del receptor de células-T (TCR). Cuando el receptor de células-T se acopla con el antígeno específico presentado por la MHC, la Lck actúa para fosforilar las cadenas intracelulares de CD3 y las cadenas-ζ del complejo TCR, lo cual permite que otra cinasa de tirosina citoplásmica denominada como ZAP-70 se enlace a ellas. Entonces la Lck fosforila y activa ZAP-70, que a su vez fosforila otra molécula en la cascada de señalización denominada como LAT (corta para el Enlazador de Células-T Activadas), una proteína transmembrana que sirve como un sitio de atraque para un número de otras proteínas, las más importantes de las cuales son Shc-Grb2-SOS, PI3K, y fosfolipasa C (PLC).

La cascada de fosforilación de tirosina iniciada por la Lck culmina en la movilización intracelular de los iones de calcio (Ca^{2+}) y en la activación de las importantes cascadas de señalización dentro del linfocito. Éstas incluyen la senda de Ras-MEK-ERK, que sigue adelante para activar ciertos factores de transcripción, tales como NFAT, NFκB, y AP-1. Estos factores de transcripción regulan la

producción de un gran número de productos genéticos, más notables las citoquinas, tales como la Interleucina-2, que promueven la proliferación y diferenciación a largo plazo de los linfocitos activados.

La tirosina Lck fosforila un número de las proteínas, las más importantes de las cuales son el receptor de CD3, ZAP-70, SLP-76, el receptor de IL-2, la cinasa C de proteína, ITK, PLC, SHC, RasGAP, Cbl, Vav1, y PI3K.

Cinasas de Lípido

Cinasa-PI3 (PIKK)

La senda de cinasa de fosfatidil-inositol-3'-OH (PI3K) es una de las sendas de señalización centrales que ejerce su efecto sobre numerosas funciones celulares, incluyendo el progreso del ciclo celular, la proliferación, la movilidad, el metabolismo, y la sobrevivencia. Una activación de las cinasas de tirosina receptoras hace que la PI3K fosforile el fosfatidil-inositol-(4,5)-difosfato, lo cual da como resultado el fosfatidil-inositol-(3,4,5)-trifosfato enlazado a membrana. Éste último promueve la transferencia de una variedad de cinasas de proteína desde el citoplasma hasta la membrana de plasma, mediante el enlace del fosfatidil-inositol-(3,4,5)-trifosfato al dominio de cinasa de homología de pleckstrina (PH). Las cinasas que son los objetivos clave corriente abajo de PI3K incluyen la cinasa dependiente de fosfoinositida 1 (PDK1) y la AKT (también conocida como cinasa B de proteína). La fosforilación de estas cinasas entonces permite la activación o desactivación de otras

numerosas sendas, que involucran a mediadores tales como GSK3, mTOR, PRAS40, FKHD, NF-κB, BAD, Caspasa-9, y similares. Un mecanismo de retroalimentación negativo importante para la senda de PI3K es PTEN, una fosfatasa que cataliza la desfosforilación del fosfatidil-inositol-(3,4,5)-trifosfato para fosforilar el fosfatidil-inositol-(4,5)-difosfato. En más del 60 por ciento de todos los tumores sólidos, PTEN se muta en una forma inactiva, que permite una activación constitutiva de la senda de PI3K. Debido a que la mayoría de los cánceres son tumores sólidos, esta observación proporciona evidencia de que la dirección de la PI3K misma o de las cinasas individuales corriente abajo en la senda de PI3K, proporciona un planteamiento prometedor para mitigar o inclusive abolir la mala regulación en muchos cánceres y, por consiguiente, restablecer la función y el comportamiento celular normal. Esto, sin embargo, no excluye que otros mecanismos puedan ser responsables de los efectos benéficos de los agentes modificadores de la actividad de PI3K, tales como los compuestos proporcionados en la presente.

En ciertas modalidades, los compuestos y las sales farmacéuticamente aceptables y solvatos de los mismos proporcionados en la presente, inhiben la actividad de las cinasas de lípido, tales como la cinasa-PI3 y/o los miembros de la familia de cinasa de proteína relacionada con la cinasa-PI3 (también denominada como PIKK, e incluyen DNA-PK, ATM, ATR, hSMG-1 y mTOR), tales como la cinasa de proteína de ADN. Estos compuestos y las sales farmacéuticamente aceptables y solvatos de los mismos,

son útiles en el tratamiento de las condiciones que sean mediadas por la activación (incluyendo la actividad normal o en especial la sobre-actividad) de uno o más de los miembros de la familia de cinasa PI3, en especial la enzima de cinasa PI3, tales como las condiciones proliferativas, inflamatorias o alérgicas, las enfermedades obstructivas de las vías respiratorias, y/o los trastornos que se presentan comúnmente en relación con los trasplantes.

De acuerdo con lo anterior, la presente invención proporciona además un método para prevenir o tratar cualquiera de las enfermedades o trastornos descritos anteriormente, en un sujeto que necesite dicho tratamiento, cuyo método comprende administrar a este sujeto, una cantidad terapéuticamente efectiva (véase, *"Administración y composiciones farmacéuticas"*, más adelante) de un compuesto de la fórmula I o de una sal farmacéuticamente aceptable del mismo. Para cualquiera de los usos anteriores, la dosificación requerida variará dependiendo del modo de administración, de la condición particular que se vaya a tratar, y del efecto deseado.

Vías de Administración y Composiciones Farmacéuticas

Para los usos terapéuticos de los compuestos de la fórmula (I), o de las sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, descritos en la presente, estos compuestos se administran en cantidades terapéuticamente efectivas ya sea solos o bien como parte de una composición

farmacéutica. De conformidad con lo anterior, en la presente se proporcionan composiciones farmacéuticas, las cuales comprenden cuando menos un compuesto de la fórmula (I) descrito en la presente, sales farmacéuticamente aceptables y/o solvatos del mismo, y uno o más vehículos, diluyentes, o excipientes farmacéuticamente aceptables. En adición, estos compuestos y composiciones se administran individualmente o en combinación con uno o más agentes terapéuticos adicionales. Las vías de administración de los compuestos de la fórmula (I) y de las composiciones farmacéuticas incluyen, pero no se limitan a, administración oral, administración intravítrea, administración rectal, administración parenteral, administración intravenosa, administración intraperitoneal, administración intramuscular, inhalación, administración transmucosal, administración pulmonar, administración intestinal, administración subcutánea, administración intramedular, administración intratecal, administración intraventricular directa, administración intranasal, administración tópica, administración oftálmica, o administración ótica.

En ciertas modalidades, los compuestos de la fórmula (I) o las composiciones farmacéuticas descritas en la presente, se administran localmente, mientras que en otras modalidades, los compuestos de la fórmula (I) o las composiciones farmacéuticas descritas en la presente, se administran sistémicamente. La administración local incluye, pero no se limita a, inyección en un órgano, opcionalmente en una formulación de depósito o de

liberación sostenida. La administración sistémica incluye, pero no se limita a, administración oral o administración intravenosa. En otras modalidades, los compuestos de la fórmula (I) o las composiciones farmacéuticas descritas en la presente, se administran en un sistema de suministro dirigido de fármacos, tal como, a manera de ejemplo solamente, en un liposoma recubierto con anticuerpo específico del órgano. El liposoma se dirige hacia, y es selectivamente absorbido por, el órgano. En otras modalidades, los compuestos de la fórmula (I) o las composiciones farmacéuticas descritas en la presente, se administran en la forma de una formulación de liberación rápida, mientras que en otras modalidades, los compuestos de la fórmula (I) o las composiciones farmacéuticas descritas en la presente, se administran en la forma de una formulación de liberación prolongada. En otras modalidades, los compuestos de la fórmula (I) o las composiciones farmacéuticas descritas en la presente, se administran en la forma de una formulación de liberación intermedia.

La cantidad terapéuticamente efectiva variará dependiendo, entre otras cosas, de la enfermedad indicada, de la gravedad de la enfermedad, de la edad y salud relativa del sujeto, de la potencia del compuesto administrado, de la vía de administración, y del tratamiento deseado. En ciertas modalidades, se indica que se obtienen resultados satisfactorios con dosificaciones diarias de un compuesto de la fórmula (I) de aproximadamente 0.03 a 2.5 miligramos/kilogramo de peso corporal. En ciertas modalidades, la dosificación diaria de un compuesto de la fórmula (I) administrado

oralmente, está en el intervalo de 0.05 microgramos por kilogramo de peso corporal (µg/kg) a 100 microgramos por kilogramo de peso corporal (µg/kg). En ciertas modalidades, la dosificación diaria de un compuesto de la fórmula (I) administrado tópicamente, está en el intervalo de 0.05 microgramos por kilogramo de peso corporal (µg/kg) a 100 microgramos por kilogramo de peso corporal (µg/kg). En otras modalidades, la dosificación diaria de un compuesto de la fórmula (I) administrado parenteralmente, está en el intervalo de 0.05 microgramos por kilogramo de peso corporal (µg/kg) a 100 miligramos por kilogramo de peso corporal (mg/kg). En ciertas modalidades, la dosificación diaria de un compuesto de la fórmula (I) administrado intramuscularmente, está en el intervalo de 0.05 microgramos por kilogramo de peso corporal (µg/kg) a 100 microgramos por kilogramo de peso corporal (µg/kg). Una dosificación diaria indicada en el mamífero superior, por ejemplo, en los seres humanos, está en el intervalo de aproximadamente 0.5 miligramos a aproximadamente 100 miligramos de un compuesto de la fórmula (I), convenientemente administrados, por ejemplo, en dosis divididas hasta cuatro veces al día, o en una forma de liberación controlada. En cierta modalidad, las formas de dosificación unitaria para su administración oral comprenden de aproximadamente 1 a 50 miligramos de un compuesto de la fórmula (I).

Otros aspectos proporcionados en la presente son los procesos para la preparación de una composición farmacéutica que comprende

cuando menos un compuesto de la fórmula (I) descrito en la presente. En ciertas modalidades, estos procesos incluyen mezclar un compuesto de la fórmula (I) descrito en la presente, con uno o más vehículos, diluyentes, o excipientes farmacéuticamente aceptables. En ciertas modalidades, las composiciones farmacéuticas comprenden un compuesto de la fórmula (I) en forma libre o en una forma de sal o de solvato farmacéuticamente aceptable. En ciertas modalidades, las composiciones farmacéuticas que comprenden un compuesto de la fórmula (I) en forma libre o en una forma de sal o de solvato farmacéuticamente aceptable, en asociación con cuando menos un vehículo, diluyente, o excipiente farmacéuticamente aceptable, se fabrican mediante procesos de mezcla, disolución, granulación, elaboración de grageas, levigación, emulsión, encapsulación, atrape o compresión, y/o mediante métodos de recubrimiento. En otras modalidades, estas composiciones are opcionalmente contienen excipientes, tales como agentes conservadores, estabilizantes, humectantes o emulsionantes, promotores de solución, sales para regular la presión osmótica y/o reguladores del pH. En otras modalidades, estas composiciones se esterilizan.

Formas de Dosificación Oral

En ciertas modalidades, las composiciones farmacéuticas que contienen cuando menos un compuesto de la fórmula (I), se administran oralmente como formas de dosificación separadas, en donde estas formas de dosificación incluyen, pero no se limitan a,

cápsulas, cápsulas de gelatina, caplets, tabletas, tabletas masticables, polvos, píldoras, grageas, gránulos, líquidos, geles, jarabes, jarabes saborizados, elíxires, pastas acuosas, soluciones o suspensiones en líquidos acuosos o no acuosos, espumas o batidos comestibles, y emulsiones líquidas de aceite en agua o emulsiones líquidas de agua en aceite. Las cápsulas, cápsulas de gelatina, caplets, tabletas, tabletas masticables, polvos o gránulos, utilizados para la administración oral de cuando menos un compuesto de la fórmula (I), se preparan mediante la mezcla de cuando menos un compuesto de la fórmula (I), (ingrediente activo) junto con cuando menos un excipiente, empleando técnicas de composición farmacéutica convencionales. Los ejemplos no limitantes de los excipientes utilizados en las formas de dosificación oral descritas en la presente incluyen, pero no se limitan a, aglutinantes, rellenos, desintegrantes, lubricantes, absorbentes, colorantes, saborizantes, conservadores, y edulcorantes.

Los ejemplos no limitantes de los aglutinantes incluyen, pero no se limitan a, almidón de maíz, almidón de papa, pasta de almidón, almidón pregelatinizado, u otros almidones, azúcares, gelatina, gomas naturales y sintéticas, tales como acacia, alginato de sodio, ácido algínico, otros alginatos, tragacanto, goma guar, celulosa y sus derivados (a manera de ejemplo solamente, etil-celulosa, acetato de celulosa, carboxi-metil-celulosa de calcio, carboxi-metil-celulosa de sodio, metil-celulosa, hidroxi-propil-metil-celulosa, y celulosa microcristalina), silicato de magnesio y aluminio, polivinil-pirrolidona,

y combinaciones de los mismos.

Los ejemplos no limitantes de los rellenos incluyen, pero no se limitan a, talco, carbonato de calcio (por ejemplo, gránulos o polvo), celulosa microcristalina, celulosa en polvo, dextratos, caolín, manitol, ácido silícico, sorbitol, almidón, almidón pregelatinizado, y mezclas de los mismos. En ciertas modalidades, el aglutinante o relleno en las composiciones farmacéuticas proporcionadas en la presente, están presentes en de aproximadamente el 50 a aproximadamente el 99 por ciento en peso de la composición farmacéutica o forma de dosificación.

Los ejemplos no limitantes de los desintegrantes incluyen, pero no se limitan a, agar-agar, ácido algínico, alginato de sodio, carbonato de calcio, carbonato de sodio, celulosa microcristalina, croscarmelosa de sodio, crospovidona, poliacrilina de potasio, glicolato de almidón de sodio, almidón de papa o tapioca, almidón pregelatinizado, otros almidones, arcillas, otros alginos, otras celulosas, gomas, y combinaciones de los mismos. En ciertas modalidades, la cantidad de desintegrante utilizada en las composiciones farmacéuticas proporcionadas en la presente, es de aproximadamente el 0.5 a aproximadamente el 15 por ciento en peso de desintegrante, mientras que en otras modalidades, la cantidad es de aproximadamente el 1 a aproximadamente el 5 por ciento en peso de desintegrante.

Los ejemplos no limitantes de los lubricantes incluyen, pero no se limitan a, estearato de sodio, estearato de calcio, estearato de

magnesio, ácido esteárico, aceite mineral, aceite mineral ligero, glicerina, sorbitol, manitol, polietilenglicol, otros glicoles, lauril-sulfato de sodio, talco, aceite vegetal hidrogenado (a manera de ejemplo solamente, aceite de cacahuate, aceite de semilla de algodón, aceite de girasol, aceite de ajonjolí, aceite de oliva, aceite de maíz, y aceite de semilla de soya), estearato de zinc, oleato de sodio, oleato de etilo, laureato de etilo, agar, sílice, gel de sílice siloide (AEROSIL 200, fabricado por W.R. Grace Co. de Baltimore, Md.), un aerosol coagulado de sílice sintética (comerciado por Degussa Co. de Plano, Tex.), CAB-O-SIL (un producto de dióxido de silicio pirogénico vendido por Cabot Co. de Boston, Mass.), y combinaciones de los mismos. En ciertas modalidades, la cantidad de lubricantes utilizados en las composiciones farmacéuticas proporcionadas en la presente, es una cantidad de menos de aproximadamente el 1 por ciento en peso de las composiciones farmacéuticas o formas de dosificación.

Los ejemplos no limitantes de los diluyentes incluyen, pero no se limitan a, lactosa, dextrosa, sacarosa, manitol, sorbitol, celulosa, glicina, o combinaciones de los mismos.

En ciertas modalidades, las tabletas y cápsulas se preparan mediante la mezcla uniforme de cuando menos un compuesto de la fórmula (I) (ingredientes activos) con vehículos líquidos, vehículos sólidos finamente divididos, o ambos, y entonces se configura el producto en la presentación deseada, si es necesario. En ciertas modalidades, las tabletas se preparan mediante compresión. En

otras modalidades, las tabletas se preparan mediante moldeo.

En ciertas modalidades, cuando menos un compuesto de la fórmula (I) se administra oralmente como una forma de dosificación de liberación controlada. Estas formas de dosificación se utilizan para proporcionar una liberación lenta o controlada de uno o más de los compuestos de la fórmula (I). La liberación controlada se obtiene utilizando, por ejemplo, hidroxi-propil-metil-celulosa, otras matrices poliméricas, geles, membranas permeables, sistemas osmóticos, recubrimientos en múltiples capas, micropartículas, liposomas, microesferas, o una combinación de los mismos. En ciertas modalidades, las formas de dosificación de liberación controlada se utilizan para prolongar la actividad del compuesto de la fórmula (I), para reducir la frecuencia de dosificación, y para aumentar el cumplimiento del paciente.

La administración de los compuestos de la fórmula (I), como fluidos orales, tales como soluciones, jarabes y elíxires, se preparan en formas de dosificación unitaria, de tal manera que una cantidad dada de soluciones, jarabes o elíxires, contiene una cantidad previamente determinada 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 un vehículo alcohólico no tóxico. Las suspensiones se formulan mediante la dispersión del compuesto en un vehículo no tóxico. Los ejemplos no limitantes de los excipientes utilizados como fluidos orales para administración

238

oral incluyen, pero no se limitan a, solubilizantes, emulsionantes, agentes saborizantes, conservadores, y agentes colorantes. Los ejemplos no limitantes de los solubilizantes y emulsionantes incluyen, pero no se limitan a, agua, glicoles, aceites, alcoholes, alcoholes isoestearílicos etoxilados, y éteres de sorbitol de polioxietileno. Los ejemplos no limitantes de los conservadores incluyen, pero no se limitan a, benzoato de sodio. Los ejemplos no limitantes de los agentes saborizantes incluyen, pero no se limitan a, aceite de hierbabuena o edulcorantes naturales, o sacarina u otros edulcorantes artificiales.

Formas de Dosificación Parenteral

En ciertas modalidades, las composiciones farmacéuticas que contienen cuando menos un compuesto de la fórmula (I) se administran parenteralmente por diferentes vías, incluyendo, pero no limitándose a, subcutánea, intravenosa (incluyendo inyección de bolo), intramuscular, e intra-arterial.

Estas formas de dosificación parenteral se administran en la forma de soluciones inyectables estériles o esterilizables, suspensiones, productos secos y/o liofilizados listos para disolverse o suspenderse en un vehículo farmacéuticamente aceptable para inyección (polvos reconstituibles), y emulsiones. Los vehículos utilizados en estas formas de dosificación incluyen, pero no se limitan a, agua para inyección USP; vehículos acuosos, tales como, pero no limitándose a, inyección de cloruro de sodio, regulador de solución salina fisiológica, solución de inyección de Ringer,

inyección de dextrosa, inyección de dextrosa y cloruro de sodio, y solución lactatada de inyección de Ringer; vehículos miscibles en agua, tales como, pero no limitándose a, alcohol etílico, polietilenglicol, y polipropilenglicol; y vehículos no acuosos, tales como, pero no limitándose a, aceite de maíz, aceite de semilla de algodón, aceite de cacahuate, aceite de ajonjolí, oleato de etilo, miristato de isopropilo, y benzoato de bencilo.

En ciertas modalidades, un compuesto de la fórmula (I) o una composición que contenga uno o más compuestos de la fórmula (I), se administra parenteralmente mediante inyección de bolo. En otras modalidades, un compuesto de la fórmula (I) o una composición que contenga uno o más compuestos de la fórmula (I) se administra parenteralmente mediante infusión continua. Las formulaciones para inyección se presentan en una forma de dosificación unitaria; a manera de ejemplo solamente, en las ampolletas o formulaciones para inyección, se presentan en recipientes de múltiples dosis, con un conservador añadido. Las composiciones pueden tomar formas tales como suspensiones, soluciones, o emulsiones en vehículos oleosos o acuosos, y pueden contener agentes de formulación, tales como agentes de suspensión, estabilizantes, y/o dispersantes.

Administración Transdérmica

En ciertas modalidades, las composiciones farmacéuticas que contienen cuando menos un compuesto de la fórmula (I), se administran transdérmicamente. Estas formas de dosificación transdérmica incluyen parches de "tipo depósito" o "tipo matriz", que

se aplican a la piel y se usan durante un período de tiempo específico para permitir la penetración de una cantidad deseada de un compuesto de la fórmula (I). A manera de ejemplo solamente, estos dispositivos transdérmicos están en la forma de un parche que comprende un miembro de respaldo, un depósito que contiene el compuesto opcionalmente con vehículos, opcionalmente una barrera de control de velocidad para suministrar el compuesto a la piel del huésped a una velocidad controlada y previamente determinada durante un período de tiempo prolongado, y elementos para asegurar el dispositivo a la piel. En otras modalidades, se utilizan formulaciones transdérmicas de matriz. En ciertas modalidades, se utiliza la administración transdérmica para proporcionar una infusión continua, mientras que en otras modalidades, se utiliza la administración transdérmica para proporcionar una infusión discontinua de un compuesto de la fórmula (I) en cantidades controladas.

En ciertas modalidades, la velocidad de absorción se hace más lenta utilizando membranas de control de velocidad o atrapando el compuesto dentro de una matriz polimérica o un gel. En ciertas modalidades, el suministro transdérmico es por medio de un parche transdérmico.

Las formulaciones para suministro transdérmico de un compuesto de la fórmula (I), incluyen una cantidad efectiva de un compuesto de la fórmula (I), un vehículo, y un diluyente opcional. Un vehículo incluye, pero no se limita a, solventes farmacológicamente

aceptables absorbibles para ayudar al paso a través de la piel del huésped, tales como agua, acetona, etanol, etilen-glicol, propilenglicol, butano-1,3-diol, miristato de isopropilo, palmitato de isopropilo, aceite mineral, y combinaciones de los mismos.

En ciertas modalidades, los sistemas de suministro transdérmico incluyen potenciadores de penetración para ayudar a suministrar uno o más compuestos de la fórmula (I), al tejido. Estos potenciadores de penetración incluyen, pero no se limitan a, acetona; diferentes alcoholes, tales como etanol, oleílo, y tetrahidro-furilo; sulfóxidos de alquilo, tales como sulfóxido de dimetilo; dimetil-acetamida; dimetil-formamida; polietilenglicol; pirrolidonas, tales como polivinil-pirrolidona; los grados Kollidon (Povidona, Polividona); urea; y diferentes ésteres de azúcar solubles o insolubles en agua, tales como Tween 80 (polisorbato 80) y Span 60 (monoestearato de sorbitán).

En otras modalidades, el pH de esta composición farmacéutica o forma de dosificación transdérmica, o del tejido al que se aplica la composición farmacéutica o la forma de dosificación, se ajusta para mejorar el suministro de uno o más compuestos de la fórmula (I). En otras modalidades, se ajustan la polaridad de un vehículo solvente, su concentración iónica, o la tonicidad, para mejorar el suministro. En otras modalidades, los compuestos, tales como estearatos, se agregan para alterar convenientemente la hidrofilicidad o lipofilicidad de uno o más compuestos de la fórmula (I), con el fin de mejorar el suministro. En ciertas modalidades, los estearatos sirven como un

vehículo de lípido para la formulación, como un agente emulsionante o tensoactivo, y como un agente mejorador del suministro o potenciador de la penetración. En otras modalidades, se utilizan diferentes sales, hidratos o solvatos de los compuestos de la fórmula (I), para ajustar adicionalmente las propiedades de la composición resultante.

En otras modalidades, el suministro transdérmico del compuesto de la fórmula (I) se lleva a cabo por medio de parches iontoforéticos y similares.

Forma de Dosificación Tópica

En ciertas modalidades, se administra cuando menos un compuesto de la fórmula (I), mediante la aplicación tópica de la composición farmacéutica que contiene cuando menos un compuesto de la fórmula (I), en la 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. Estas formulaciones contienen de una manera opcional, solubilizantes, estabilizantes, agentes mejoradores de la tonicidad, reguladores del pH, y conservadores.

Las formulaciones tópicas incluyen cuando menos un vehículo, y opcionalmente cuando menos un diluyente. Estos vehículos y diluyentes incluyen, pero no se limitan a, agua, acetona, etanol, etilenglicol, propilenglicol, butano-1,3-diol, miristato de isopropilo,

palmitato de isopropilo, aceite mineral, y combinaciones de los mismos.

En ciertas modalidades, estas formulaciones tópicas incluyen potenciadores de la penetración para ayudar a suministrar uno o más compuestos de la fórmula (I), al tejido. Estos potenciadores de la penetración incluyen, pero no se limitan a, acetona; diferentes alcoholes, tales como etanol, oleílo, y tetrahidro-furilo; sulfóxidos de alquilo, tales como sulfóxido de dimetilo; dimetil-acetamida; dimetil-formamida; polietilenglicol; pirrolidonas, tales como polivinil-pirrolidona; los grados Kollidon (Povidona, Polividona); urea; y diferentes ésteres de azúcar solubles e insolubles en agua, tales como Tween 80 (polisorbato 80) y Span 60 (monoestearato de sorbitán).

Administración Pulmonar

En ciertas modalidades, las composiciones farmacéuticas que contienen cuando menos un compuesto de la fórmula (I), se administran mediante inhalación. Las formas de dosificación para administración inhalada se formulan como aerosoles o polvos secos. Las formulaciones en aerosol para administración mediante inhalación comprenden una solución o suspensión fina de cuando menos un compuesto de la fórmula (I), en un solvente acuoso o no acuoso farmacéuticamente aceptable. En adición, estas composiciones farmacéuticas opcionalmente comprenden una base de polvo, tal como lactosa, glucosa, trehalosa, manitol, o almidón, y opcionalmente un modificador del desempeño, tal como L-leucina u

241

otro aminoácido, y/o sales de metales de ácido esteárico, tales como estearato de magnesio o de calcio.

En ciertas modalidades, los compuestos de la fórmula (I), se van a administrar directamente al pulmón mediante inhalación utilizando un Inhalador de Dosis Medida ("MDI"), el cual utiliza latas que contienen un propelente de bajo punto de ebullición adecuado, por ejemplo, dicloro-difluoro-metano, tricloro-fluoro-metano, dicloro-tetrafluoro-etano, dióxido de carbono, u otro gas adecuado, o un dispositivo Inhalador de Polvo Seco (DPI), el cual utiliza una ráfaga de gas para crear una nube de polvo seco dentro de un recipiente, el cual entonces es inhalado por el paciente. En ciertas modalidades, se formulan cápsulas y cartuchos de gelatina para utilizarse en un inhalador o insuflador, que contienen una mezcla en polvo de un compuesto de la fórmula (I), y una base de polvo, tal como lactosa o almidón. En ciertas modalidades, los compuestos de la fórmula (I), se suministran al pulmón utilizando un dispositivo rociador de líquido, en donde estos dispositivos utilizan orificios de boquillas extremadamente pequeños para aerosolizar las formulaciones de fármaco líquidas, las cuales entonces pueden ser inhaladas directamente hacia el pulmón. En otras modalidades, los compuestos de la fórmula (I), se suministran al pulmón utilizando un dispositivo nebulizador, en donde un nebulizador crea un aerosol de las formulaciones de fármaco líquidas utilizando energía ultrasónica para formar partículas finas que pueden ser fácilmente inhaladas. En otras modalidades, los compuestos de la fórmula (I), se suministran

al pulmón utilizando un dispositivo de aerosol electrohidrodinámico ("EHD"), en donde estos dispositivos de aerosol electro-hidrodinámicos utilizan energía eléctrica para aerosolizar las soluciones o suspensiones de fármaco líquidas.

En ciertas modalidades, la composición farmacéutica que contiene cuando menos un compuesto de la fórmula (I), o sales farmacéuticamente aceptables y solvatos del mismo, descrita en la presente, también contiene uno o más potenciadores de absorción. En ciertas modalidades, estos potenciadores de absorción incluyen, pero no se limitan a, glicocolato de sodio, caprato de sodio, N-lauril-ß-D-maltopiranosida, EDTA, y micelios mixtos.

En ciertas modalidades, las composiciones farmacéuticas que contienen cuando menos un compuesto de la fórmula (I), se administran nasalmente. Las formas de dosificación para administración nasal se formulan como aerosoles, soluciones, gotas, geles, o polvos secos.

Administración Rectal

En ciertas modalidades, las composiciones farmacéuticas que contienen cuando menos un compuesto de la fórmula (I), se administran rectalmente en la forma de supositorios, enemas, enemas de retención, ungüento, cremas, espumas rectales, o geles rectales. En ciertas modalidades, los supositorios se preparan a partir de emulsiones o suspensiones grasas, manteca de cacao, u otros glicéridos.

242

Administración de Depósito

En ciertas modalidades, las composiciones farmacéuticas que contienen cuando menos un compuesto de la fórmula (I) se formulan como una preparación de depósito. Estas formulaciones de larga acción se administran mediante implantación (por ejemplo, subcutáneamente o intramuscularmente) o mediante inyección intramuscular. En ciertas modalidades, estas formulaciones incluyen materiales poliméricos o hidrofóbicos (por ejemplo, como una emulsión en un aceite aceptable), o resinas de intercambio de iones, o como derivados escasamente solubles, por ejemplo, como una sal escasamente soluble.

En ciertas modalidades, las formas de depósito inyectables se hacen mediante la formación de matrices microencapsuladas del compuesto de la fórmula (I) en polímeros biodegradables. La velocidad en que se libera el compuesto de la fórmula (I) se controla variando la proporción del compuesto de la fórmula (I) al polímero, y la naturaleza del polímero particular empleado. En otras modalidades, las formulaciones de depósito inyectables se preparan atrapando el compuesto de la fórmula (I) en liposomas o en microemulsiones.

Administración Oftálmica

En ciertas modalidades, un compuesto de la fórmula (I) o una composición farmacéutica descrita en la presente, se administra oftálmicamente a los ojos. La administración a los ojos, en términos

generales, da como resultado el contacto directo de los agentes con la córnea, a través de la cual pasa cuando menos una porción de los agentes administrados. En ciertas modalidades, estos compuestos de la fórmula (I) o las composiciones farmacéuticas, tienen un tiempo de residencia efectivo en el ojo de aproximadamente 2 a aproximadamente 24 horas. En ciertas modalidades, estos compuestos de la fórmula (I) o las composiciones farmacéuticas, tienen un tiempo de residencia efectivo en el ojo de aproximadamente 4 a aproximadamente 24 horas. En ciertas modalidades, estos compuestos de la fórmula (I) o las composiciones farmacéuticas, tienen un tiempo de residencia efectivo en el ojo de aproximadamente 6 a aproximadamente 24 horas.

Administración oftálmica, como se utiliza en la presente, incluye, pero no se limita a, administración tópica, inyección intraocular, inyección sub-retinal, inyección intravítrea, administración periocular, inyecciones sub-conjuntivales, inyecciones retrobulbares, inyecciones intracamerales (incluyendo en la cámara anterior o vítrea), inyecciones o implantes de sub-tenon, soluciones oftálmicas, suspensiones oftálmicas, ungüentos oftálmicos, implantes oculares e insertos oculares, soluciones intraoculares, el uso de iontoforesis, incorporación en soluciones irrigadoras quirúrgicas, y paquetes (a manera de ejemplo solamente, un algodón saturado insertado en el fórnix). En ciertas modalidades, los compuestos de la fórmula (I) o las composiciones farmacéuticas descritas en la presente, se formulan como una composición oftálmica, y se

administran tópicamente a los ojos. Estas composiciones oftálmicas tópicamente administradas incluyen, pero no se limitan a, soluciones, suspensiones, geles, o ungüentos.

En ciertas modalidades, las composiciones farmacéuticas que comprenden cuando menos un compuesto de la fórmula (I) descrito en la presente, utilizadas para su administración oftálmica, toman la forma de un líquido, en donde las composiciones están presentes en solución, en suspensión, o ambas. En algunas modalidades, una composición líquida incluye una formulación de gel. En otras modalidades, la composición líquida es acuosa. En otras modalidades, estas composiciones líquidas toman la forma de un ungüento. En ciertas modalidades, las composiciones farmacéuticas que contienen cuando menos un compuesto de la fórmula (I) se administran oftálmicamente como gotas para los ojos formuladas como soluciones acuosas que opcionalmente contienen solubilizantes, estabilizantes, agentes mejoradores de la tonicidad, reguladores, y conservadores. Una dosificación deseada se administra por medio de un número conocido de gotas en el ojo. A manera de ejemplo solamente, para un volumen de una gota de 25 microlitros, la administración de 1 a 6 gotas proporciona de 25 a 150 microlitros de la composición. En ciertas modalidades, las composiciones acuosas contienen de aproximadamente el 0.01 por ciento a aproximadamente el 50 por ciento en peso/volumen de un compuesto de la fórmula (I). En otras modalidades, las composiciones acuosas contienen de aproximadamente el 0.1 por

ciento a aproximadamente el 20 por ciento en peso/volumen de un compuesto de la fórmula (I). En todavía otras modalidades, las composiciones acuosas contienen de aproximadamente el 0.2 por ciento a aproximadamente el 10 por ciento en peso/volumen de un compuesto de la fórmula (I). En ciertas modalidades, las composiciones acuosas contienen de aproximadamente el 0.5 por ciento a aproximadamente el 5 por ciento en peso/volumen de un compuesto de la fórmula (I).

En ciertas modalidades, las composiciones acuosas tienen un pH y una osmolaridad oftálmicamente aceptables. En ciertas modalidades, las composiciones acuosas incluyen uno o más agentes de ajuste del pH o agentes reguladores oftálmicamente aceptables, incluyendo ácidos, tales como ácido acético, bórico, cítrico, láctico, fosfórico y clorhídrico; bases, tales como hidróxido de sodio, fosfato de sodio, borato de sodio, citrato de sodio, acetato de sodio, lactato de sodio, y tris-hidroxi-metil-amino-metano; y reguladores, tales como citrato/dextrosa, bicarbonato de sodio, y cloruro de amonio. Estos ácidos, bases y reguladores se incluyen en una cantidad requerida para mantener el pH de la composición en un intervalo oftálmicamente aceptable.

En ciertas modalidades, las composiciones también incluyen una o más sales oftálmicamente aceptables en una cantidad requerida para llevar la osmolaridad de la composición hasta un intervalo oftálmicamente aceptable. Estas sales incluyen aquéllas que tienen cationes de sodio, potasio o amonio, y aniones de cloruro,

citrato, ascorbato, borato, fosfato, bicarbonato, sulfato, tiosulfato o bisulfito; las sales adecuadas incluyen cloruro de sodio, cloruro de potasio, tiosulfato de sodio, bisulfito de sodio, y sulfato de amonio.

En ciertas modalidades, las composiciones acuosas también contienen uno o más polímeros como agentes de suspensión. Estos polímeros incluyen, pero no se limitan a, polímeros solubles en agua, tal como los polímeros celulósicos descritos en la presente, (como ejemplo solamente, hidroxi-propil-metil-celulosa), y los polímeros insolubles en agua descritos en la presente (como ejemplo solamente, polímeros reticulados que contienen carboxilo). En ciertas modalidades, las composiciones acuosas también incluyen un polímero mucoadhesivo oftálmicamente aceptable, seleccionado, por ejemplo, a partir de carboxi-metil-celulosa, carbómero (polímero de ácido acrílico), poli-(metacrilato de metilo), poli-acrilamida, poli-carbofil, copolímero de ácido acrílico/acrilato de butilo, alginato de sodio, y dextrano.

En ciertas modalidades, las composiciones también incluyen agentes solubilizantes oftálmicamente aceptables para ayudar en la solubilidad de un compuesto de la fórmula (I). El término "agente solubilizante", en términos generales, incluye los agentes que dan como resultado la formación de una solución micelar o una solución verdadera del agente. En ciertas modalidades, se utilizan tensoactivos no iónicos oftálmicamente aceptables, incluyendo, pero no limitándose a, polisorbato 80, como agentes solubilizantes. En otras modalidades, se utilizan glicoles oftálmicamente aceptables,

incluyendo, pero no limitándose a, poliglicoles, polietilenglicol 400, y glicol-éteres, como agentes solubilizantes.

En ciertas modalidades, las composiciones también incluyen uno o más tensoactivos oftálmicamente aceptables para mejorar la estabilidad física o para otros propósitos. Estos tensoactivos no iónicos incluyen, pero no se limitan a, glicéridos de ácidos grasos de polioxietileno y aceites vegetales (a manera de ejemplo solamente, aceite de ricino hidrogenado de polioxietileno (60)), y alquil-éteres y alquil-fenil-éteres de polioxietileno (a manera de ejemplo solamente, octoxinol 10 y octoxinol 40).

En ciertas modalidades, las composiciones también incluyen uno o más conservadores oftálmicamente aceptables para inhibir la actividad microbiana. Estos conservadores incluyen, pero no se limitan a, sustancias que contienen mercurio, tales como merfeno y tiomersal; dióxido de cloro estabilizado; y compuestos de amonio cuaternario, tales como cloruro de benzalconio, bromuro de cetil-trimetil-amonio, y cloruro de cetil-piridinio.

En ciertas modalidades, las composiciones también incluyen uno o más antioxidantes para mejorar la estabilidad química cuando se requiera. Estos antioxidantes incluyen, pero no se limitan a, ácido ascórbico y metabisulfito de sodio.

En ciertas modalidades, las composiciones acuosas proporcionados en la presente se empacan en recipientes re-cerrables de una sola dosis, mientras que en otras modalidades, las composiciones acuosas proporcionados en la presente se empacan

en recipientes re-cerrables de múltiples dosis, en donde se incluye un conservador en la composición.

Administración Ótica

En ciertas modalidades, las composiciones farmacéuticas que contienen cuando menos un compuesto de la fórmula (I), se administran óticamente como gotas para los oídos. Estas formulaciones son soluciones acuosas que opcionalmente contienen solubilizantes, estabilizantes, agentes mejoradores de la tonicidad, reguladores del pH, y conservadores.

Terapias de Combinación

En ciertas modalidades, un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, o una composición farmacéutica que contiene cuando menos un compuesto de la fórmula (I), se administra solo (sin un agente terapéutico adicional) para el tratamiento de una o más de las enfermedades y/o los trastornos asociados con la actividad de cinasa de proteína de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK descritos en la presente.

En ciertas modalidades, un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, o una composición farmacéutica que contiene cuando menos un compuesto de la fórmula (I), se administra solo (sin un agente terapéutico adicional) para el tratamiento de una o más de las enfermedades y/o los trastornos

asociados con la actividad de cinasa de proteína de TrkA, TrkB, TrkC, IGF-1R, y/o ALK descritos en la presente.

En otras modalidades, un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, o una composición farmacéutica que contiene cuando menos un compuesto de la fórmula (I) proporcionado en la presente, se administra en combinación con uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y/o los trastornos asociados con la actividad de cinasa de proteína de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK descritos en la presente.

En otras modalidades, un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, o una composición farmacéutica que contiene cuando menos un compuesto de la fórmula (I) proporcionado en la presente, se administra en combinación con uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y/o los trastornos asociados con la actividad de cinasa de proteína de TrkA, TrkB, TrkC, IGF-1R y/o ALK descritos en la presente.

En otras modalidades, un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, o una composición farmacéutica que contiene cuando menos un compuesto de la fórmula (I)

proporcionado en la presente, 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/o los trastornos asociados con la actividad de cinasa de proteína de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK descritos en la presente.

En otras modalidades, un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, o una composición farmacéutica que contiene cuando menos un compuesto de la fórmula (I) proporcionado en la presente, 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/o los trastornos asociados con la actividad de cinasa de proteína de TrkA, TrkB, TrkC, IGF-1R y/o ALK descritos en la presente.

En otra modalidad, un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, o una composición farmacéutica que contiene cuando menos un compuesto de la fórmula (I) proporcionado en la presente, se administra en secuencia con uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y/o los trastornos asociados con la actividad de cinasa de proteína de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK descritos en la presente.

En otra modalidad, un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, o una composición farmacéutica que contiene cuando menos un compuesto de la fórmula (I) proporcionado en la presente, se administra en secuencia con uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y/o los trastornos asociados con la actividad de cinasa de proteína de TrkA, TrkB, TrkC, IGF-1R y/o ALK descritos en la presente.

En otras modalidades, los tratamientos de combinación proporcionados en la presente incluyen la administración de un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, o una composición farmacéutica que contiene un compuesto de la fórmula (I), antes de la administración de uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y/o los trastornos asociados con la actividad de cinasa de proteína de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK descritos en la presente.

En otras modalidades, los tratamientos de combinación proporcionados en la presente incluyen la administración de un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, o una

composición farmacéutica que contiene un compuesto de la fórmula (I), antes de la administración de uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y/o los trastornos asociados con la actividad de cinasa de proteína de TrkA, TrkB, TrkC, IGF-1R y/o ALK descritos en la presente.

En otras modalidades, los tratamientos de combinación proporcionados en la presente incluyen la administración de un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, o una composición farmacéutica que contiene un compuesto de la fórmula (I), después de la administración de uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y/o los trastornos asociados con la actividad de cinasa de proteína de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK descritos en la presente.

En otras modalidades, los tratamientos de combinación proporcionados en la presente incluyen la administración de un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, o una composición farmacéutica que contiene un compuesto de la fórmula (I), después de la administración de uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y/o los trastornos asociados con la actividad de cinasa de proteína de TrkA, TrkB, TrkC, IGF-1R y/o ALK descritos en la presente.

En otras modalidades, los tratamientos de combinación proporcionados en la presente incluyen la administración de un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, o una composición farmacéutica que contiene un compuesto de la fórmula (I), de una manera concurrente con la administración de uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y/o los trastornos asociados con la actividad de cinasa de proteína de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK descritos en la presente.

En otras modalidades, los tratamientos de combinación proporcionados en la presente incluyen la administración de un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, o una composición farmacéutica que contiene un compuesto de la fórmula (I), de una manera concurrente con la administración de uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y/o los trastornos asociados con la actividad de cinasa de proteína de TrkA, TrkB, TrkC, IGF-1R y/o ALK descritos en la presente.

En ciertas modalidades, los tratamientos de combinación proporcionados en la presente incluyen la administración de un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, o una

composición farmacéutica que contiene un compuesto de la fórmula (I), formulado con uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y/o los trastornos asociados con la actividad de cinasa de proteína de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK descritos en la presente.

En ciertas modalidades, los tratamientos de combinación proporcionados en la presente incluyen la administración de un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, o una composición farmacéutica que contiene un compuesto de la fórmula (I), formulado con uno o más agentes terapéuticos adicionales, para el tratamiento de una o más de las enfermedades y/o los trastornos asociados con la actividad de cinasa de proteína de TrkA, TrkB, TrkC, IGF-1R y/o ALK descritos en la presente.

En ciertas modalidades de los tratamientos de combinación descritos en la presente, los compuestos de la fórmula (I), o una sal farmacéuticamente aceptable o un solvato de los mismos, son moduladores de la actividad de cinasa de proteína de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK. En ciertas modalidades de los tratamientos de combinación descritos en la presente, los compuestos de la fórmula (I), o una sal farmacéuticamente aceptable o un solvato de los mismos, son inhibidores de la actividad de cinasa de proteína de TrkA, TrkB, TrkC, IGF-1R y/o ALK.

En ciertas modalidades de las terapias de combinación descritas en la presente, los compuestos de la fórmula (I) proporcionados en la presente, o una sal farmacéuticamente aceptable o un solvato de los mismos, y los agentes terapéuticos adicionales actúan de una manera aditiva. En ciertas modalidades de las terapias de combinación descritas en la presente, los compuestos de la fórmula (I) proporcionados en la presente, o una sal farmacéuticamente aceptable o un solvato de los mismos, y los agentes terapéuticos adicionales actúan de una manera sinérgica.

En otras modalidades, un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, o una composición farmacéutica que contiene un compuesto de la fórmula (I), se administra a un paciente que previamente no se haya sometido, o que actualmente no se esté sometiendo al tratamiento con otro agente terapéutico.

Los agentes terapéuticos adicionales utilizados en combinación con cuando menos un compuesto de la fórmula (I) proporcionado en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, incluyen, pero no se limitan a, agentes quimioterapéuticos, agentes anti-inflamatorios, agentes broncodilatadores, agentes anti-histamínicos, agentes descongestionantes, agentes anti-tusivos, agentes inmunomoduladores agentes anti-proliferativos, agentes citostáticos, agentes citotóxicos,

inhibidores de la biosíntesis de poliamina, inhibidores de una cinasa de proteína, inhibidores de una cinasa de proteína

serina/treonina, inhibidores de la cinasa C de proteína, inhibidores de una cinasa de proteína tirosina, inhibidores de cinasa de tirosina receptora del factor de crecimiento epidérmico (EGF) (por ejemplo, Iressa®,

inhibidores de cinasa de tirosina receptora del factor de crecimiento endotelial vascular (VEGF) (por ejemplo, PTK787 o Avastin®), inhibidores de cinasa de tirosina receptora del factor de crecimiento derivado de plaquetas (PDGF) (por ejemplo, STI571 (Glivec®)), una citoquina, un regulador de crecimiento negativo, tal como TGF-ß o IFN-ß, un inhibidor de aromatasa (por ejemplo, letrozol (Femara®) o anastrozol), un inhibidor de la interacción de un dominio SH2 con una proteína fosforilada, anti-estrógenos, bisfosfonatos (por ejemplo, AREDIA® o ZOMETA®), y anticuerpos monoclonales (por ejemplo, contra HER2, tales como trastuzumab).

Los agentes anti-inflamatorios utilizados en combinación con cuando menos un compuesto de la fórmula (I) descrito en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, incluyen, pero no se limitan a, fármacos anti-inflamatorios no esteroideos, tales como ácido salicílico, ácido acetil-salicílico, salicilato de metilo, diflunisal, salsalato, olsalazina, sulfasalazina, acetaminofeno, indometacina, sulindaco, etodolaco, ácido mefenámico, meclofenamato-sodio, tolmetina, quetorolaco, diclofenaco, ibuprofeno, naproxeno, naproxeno-sodio, fenoprofeno, quetoprofeno, flurbinprofeno, oxaprozina, piroxicam, meloxicam, ampiroxicam, droxicam, pivoxicam, tenoxicam, nabumetoma, fenil-

butazona, oxi-fenbutazona, antipirina, aminopirina, apazona y nimesulida, antagonistas de leucotrieno, incluyendo, pero no limitándose a, zileuton, aurotioglucosa, oro-tiomalato de sodio y auranofina, esteroides, incluyendo, pero no limitándose a, diproprionato de alclometasona, amcinonida, dipropionato de beclometasona, betametasona, benzoato de betametasona, diproprionato de betametasona, betametasona-fosfato de sodio, valerato de betametasona, budesonida, ciclesonida, propionato de clobetasol, pivalato de clocortolona, hidrocortisona, derivados de hidrocortisona, desonida, desoximatasona, dexametasona, flunisolida, flucoxinolida, flurandrenolida, propionato de fluticasona, glucocorticosteroides, halcinocida, medrisona, metil-prednisolona, acetato de metprednisolona, metil-prednisolona-succinato de sodio, furoato de mometasona, acetato de parametasona, prednisolona, acetato de prednisolona, prednisolona-fosfato de sodio, tebuatato de prednisolona, prednisona, triamcinolona, acetoniuro de triamcinolona, diacetato de triamcinolona, y hexacetoniuro de triamcinolona, y otros agentes anti-inflamatorios, incluyendo, pero no limitándose a, metotrexato, colquicina, alopurinol, probenecida, talidomida o un derivado de la misma, ácido 5-amino-salicílico, retinoide, ditranol o calcipotriol, sulfinpirazona, y benzobromarona.

Otros agentes anti-inflamatorios utilizados en combinación con cuando menos un compuesto de la fórmula (I) descrito en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, incluyen, pero no se limitan a, los esteroides descritos en las

250

Publicaciones Internacionales Números WO 02/88167, WO 02/12266, WO 02/100879, WO 02/00679 (en especial aquéllos de los Ejemplos 3, 11, 14, 17, 19, 26, 34, 37, 39, 51, 60, 67, 72, 73, 90, 99 y 101), en las Publicaciones Internacionales Números WO 03/35668, WO 03/48181, WO 03/62259, WO 03/64445, WO 03/72592, WO 04/39827 y WO 04/66920; agonistas del receptor glucocorticoide no esteroideos, tales como aquéllos descritos en la Patente Alemana Número DE 10261874, y en las Publicaciones Internacionales Números WO 00/00531, WO 02/10143, WO 03/82280, WO 03/82787, WO 03/86294, WO 03/104195, WO 03/101932, WO 04/05229, WO 04/18429, WO 04/19935, WO 04/26248 y WO 05/05452; antagonistas de LTB4, tales como BIIL 284, CP-195543, DPC11870, LTB4 etanolamida, LY 293111, LY 255283, CGS025019C, CP-195543, ONO-4057, SB 209247, SC-53228 y aquéllos descritos en la Patente de los Estados Unidos de Norteamérica Número US 5451700 y en la Publicación Internacional Número WO 04/108720; los antagonistas de LTD4, tales como montelukast, pranlukast, zafirlukast, accolato, SR2640, Wy-48,252, ICI 198615, MK-571, LY-171883, Ro 24-5913 y L-648051; agonistas de los receptores de dopamina, tales como cabergolina, bromocriptina, ropinirol, y 4-hidroxi-7-[2-[[2-[[3-(2-fenil-etoxi)-propil]-sulfonil]-etil]-amino]-etil]-2(3H)-benzotiazolona y las sales farmacéuticamente aceptables de la misma (en donde el clorhidrato es Viozan® - AstraZeneca); inhibidores de PDE4, tales como cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden), V-11294A (Napp),

BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofilina (Almirall Prodesfarma), PD189659 / PD168787 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene), SelCID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo), GRC 3886 (Oglemilast, Glenmark), y las Publicaciones Internacionales Números WO 92/19594, WO 93/19749, WO 93/19750, WO 93/19751, WO 99/16766, WO 01/13953, WO 03/104204, WO 03/104205, WO 04/000814, WO 04/000839 y WO 04/005258 (Merck), WO 04018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/018431, WO 04/018449, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/019944, WO 04/019945, WO 04/045607, WO 04/037805, WO 04/063197, WO 04/103998, WO 04/111044, WO 05012252, WO 05012253, WO 05/013995, WO 05/030212, WO 05/030725, WO 05/087744, WO 05/087745, WO 05/087749 y WO 05/090345, así como aquéllos descritos en las Publicaciones Internacionales Números WO 98/18796 y WO 03/39544; agonistas de A2a, tales como aquéllos descritos en las Patentes Europeas Números EP 409595A2, EP 1052264, y EP 1241176, y en las Publicaciones Internacionales Números WO 94/17090, WO 96/02543, WO 96/02553, WO 98/28319, WO 99/24449, WO 99/24450, WO 99/24451, WO 99/38877, WO 99/41267, WO 99/67263, WO 99/67264, WO 99/67265, WO 99/67266, WO 00/23457, WO 00/77018, WO 00/78774, WO 01/23399, WO 01/27130, WO 01/27131, WO 01/60835, WO 01/94368, WO 02/00676, WO 02/22630, WO 02/96462, WO 03/086408, WO 04/039762, WO

251

04/039766, WO 04/045618 y WO 04/046083; y los antagonistas de A2b, tales como aquéllos descritos en las Publicaciones Internacionales Números WO 02/42298 y WO 03/042214.

Los agentes broncodilatadores utilizados en combinación con cuando menos un compuesto de la fórmula (I) descrito en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, incluyen, pero no se limitan a, agonistas del adrenoceptor beta-2, agentes anti-colinérgicos, agentes anti-muscarínicos, bromuro de ipratropio, bromuro de oxitropio, sales de tiotropio, glicopirrolato, CHF 4226 (Chiesi), SVT-40776, albuterol (salbutamol), metaproterenol, terbutalina, salmeterol, fenoterol, procaterol, formoterol, carmoterol, y GSK159797, y las sales farmacéuticamente aceptables de los mismos.

Otros agentes broncodilatadores utilizados en combinación con cuando menos un compuesto de la fórmula (I) descrito en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, incluyen, pero no se limitan a, los compuestos (en forma libre o de sal o de solvato) de la fórmula I de la Publicación Internacional Número WO 0075114, de preferencia los compuestos de los Ejemplos de la misma, los compuestos (en forma libre o de sal o de solvato) de la fórmula I de la Publicación Internacional Número WO 04/16601 o de la fórmula I de la Publicación Internacional Número WO 04/087142, los compuestos, tales como aquéllos descritos en las Patentes Europeas Números EP 147719, EP 1440966, EP 1460064, EP 1477167, y EP 1574501, en las Patentes Japonesas Números JP

05025045 y JP 2005187357, en las Patentes de los Estados Unidos de Norteamérica Números US 2002/0055651, US 2004/0242622, US 2004/0229904, US 2005/0133417, US 2005/5159448, US 2005/ 5159448, US 2005/171147, US 2005/182091, US 2005/182092, US 2005/209227, US 2005/256115, US 2005/277632, US 2005/272769, US 2005/239778, US 2005/215542, US 2005/215590, US 2006/ 19991, US 2006/58530, en las Publicaciones Internacionales Números WO 93/18007, WO 99/64035, WO 01/42193, WO 01/83462, WO 02/66422, WO 02/ 70490, WO 02/76933, WO 03/24439, WO 03/42160, WO 03/42164, WO 03/72539, WO 03/91204, WO 03/99764, WO 04/16578, WO 04/22547, WO 04/32921, WO 04/33412, WO 04/37768, WO 04/37773, WO 04/37807, WO 04/39762, WO 04/39766, WO 04/45618 WO 04/46083, WO 04/80964, WO 04/087142, WO 04/89892, WO 04/108675, WO 04/108676, WO 05/33121, WO 05/40103, WO 05/44787, WO 05/58867, WO 05/65650, WO 05/66140, WO 05/70908, WO 05/74924, WO 05/77361, WO 05/90288, WO 05/92860, WO 05/92887, WO 05/90287, WO 05/95328, WO 05/102350, WO 06/56471, WO 06/74897, WO 06/8173, en la Patente Europea Número EP 424021, en las Patentes de los Estados Unidos de Norteamérica Números US 3714357, US 5171744, US 2005/171147, y US 2005/182091, y en las Publicaciones Internacionales Números WO 01/04118, WO 02/00652, WO 02/51841, WO 02/53564, WO 03/00840, WO 03/33495, WO 03/53966, WO 03/87094, WO 04/18422, WO 04/05285, WO 04/96800, WO 05/77361 y WO 06/48225.

252

Los agentes anti-inflamatorios y broncodilatadores dobles utilizados en combinación con cuando menos un compuesto de la fórmula (I) descrito en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, incluyen, pero no se limitan a, agonista del adrenoceptor beta-2 / antagonistas muscarínicos dobles, tales como aquéllos que se dan a conocer en las Patentes de los Estados Unidos de Norteamérica Números US 2004/0167167, US 2004/0242622, US 2005/182092, US 2005/256114, y US 2006/35933, y en las Publicaciones Internacionales Números WO 04/74246, WO 04/74812, WO 04/89892 y WO 06/23475.

Los agentes de sustancias de fármaco antihistamínicas utilizados en combinación con cuando menos un compuesto de la fórmula (I) descrito en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, incluyen, pero no se limitan a, clorhidrato de cetirizina, levocetirizina, acetaminofeno, fumarato de clemastina, prometazina, loratidina, desloratidina, difenhidramina y clorhidrato de fexofenadina, activastina, astemizol, azelastina, dimetindeno, ebastina, epinastina, levocabastina, mizolastina y tefenadina, así como los que se dan a conocer en las Publicaciones Internacionales Números WO 03/099807 y WO 04/026841, y en la Patente Japonesa Número JP 2004107299.

Los agentes inmunomoduladores utilizados en combinación con cuando menos un compuesto de la fórmula (I) descrito en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, incluyen, pero no se limitan a, azatioprina, tacrolimus,

ciclosporina, anti-malarias, metotrexato, leflunomida, corticosteroides, ciclofosfamida, ciclosporina A, ciclosporina G, micofenolato-mofetil, ascomicina, rapamicina (sirolimus), FK-506, mizoribina, 15-desoxiespergualina, brequinar, ácido micofenólico, malono-nitrilo-amidas (tales como, a manera de ejemplo solamente, leflunamida), CTLA41g, moduladores de los receptores de células-T, y moduladores de los receptores de citoquina, miméticos de péptidos, y anticuerpos (tales como, a manera de ejemplo solamente, humanos, humanizados, quiméricos, monoclonales, policlonales, fragmentos Fvs, ScFvs, Fab o $F(ab)_2$ o fragmentos de enlace de epítopos), moléculas de ácidos nucleicos (tales como, a manera de ejemplo solamente, moléculas de ácidos nucleicos anti-sentido y triples hélices), moléculas pequeñas, compuestos orgánicos, y compuestos inorgánicos. Los ejemplos de los anticuerpos monoclonales incluyen, pero no se limitan a, anticuerpos monoclonales para los receptores de leucocitos, tales como, a manera de ejemplo solamente, MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD45, CD58 o sus ligandos. Los ejemplos de los moduladores de los receptores de células-T incluyen, pero no se limitan a, anticuerpos anti-receptores de células-T (tales como, a manera de ejemplo solamente, anticuerpos anti-CD4 (tales como, a manera de ejemplo solamente, cM-T412 (Boehringer), IDEC-CE9.1^{MR} (IDEC y SKB), mAB 4162W94, Orthoclone y OKTcdr4a (Janssen-Cilag)), anticuerpos anti-CD3 (tales como, a manera de ejemplo solamente, Nuvion (Product Design Labs), OKT3 (Johnson &

Johnson), o Rituxan (IDEC)), anticuerpos anti-CD5 (tales como, a manera de ejemplo solamente, un inmunoconjugado enlazado con ricina anti-CD5), anticuerpos anti-CD7 (tales como, a manera de ejemplo solamente, CHH-380 (Novartis)), anticuerpos anti-CD8, anticuerpos monoclonales de ligandos anti-CD40 (tales como, a manera de ejemplo solamente, IDEC-131 (IDEC)), anticuerpos anti-CD52 (tales como, a manera de ejemplo solamente, CAMPATH 1H (Ilex)), anticuerpos anti-CD2, anticuerpos anti-CD11a (tales como, a manera de ejemplo solamente, Xanelim (Genentech)), anticuerpos anti-B7 (tales como, a manera de ejemplo solamente, IDEC-114 (IDEC)), CTLA4-inmunoglobulina, moduladores de los receptores tipo-Toll (TLR). Los ejemplos de los moduladores de los receptores de citoquina incluyen, pero no se limitan a, receptores de citoquina solubles (tales como, a manera de ejemplo solamente, el dominio extracelular de un receptor de TNF-α o un fragmento del mismo, el dominio extracelular de un receptor de IL-1ß o un fragmento del mismo, y el dominio extracelular de un receptor de IL-6 o un fragmento del mismo), citoquinas o fragmentos de las mismas (tales como, a manera de ejemplo solamente, interleucina (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-ß, IFN-γ, y GM-CSF), anticuerpos anti-receptores de citoquina (tales como, a manera de ejemplo solamente, anticuerpos anti-receptores de IFN, anticuerpos anti-receptores de IL-2 (tales como, a manera de ejemplo solamente, Zenapax (Protein Design Labs)), anticuerpos anti-receptores de IL-4,

anticuerpos anti-receptores de IL-6, anticuerpos anti-receptores de IL-10, y anticuerpos anti-receptores de IL-12), anticuerpos anti-citoquina (tales como, a manera de ejemplo solamente, anticuerpos anti-IFN, anticuerpos anti-TNF-α, anticuerpos anti-IL-1ß, anticuerpos anti-IL-6, anticuerpos anti-IL-8 (tales como, a manera de ejemplo solamente, ABX-IL-8 (Abgenix)), y anticuerpos anti-IL-12).

En ciertas modalidades, los agentes terapéuticos adicionales utilizados en las terapias de combinación descritas en la presente incluyen, pero no se limitan a, los agentes tales como inhibidores del factor de necrosis tumoral alfa (TNF-α) (tales como anticuerpos monoclonales anti-TNF (a manera de ejemplo solamente, Remicade, CDP-870 y adalimumab), y moléculas de inmunoglobulina de los receptores de TNF (a manera de ejemplo solamente, Enbrel, Remicade, y Humira)); inhibidores no selectivos de ciclo-oxigenasa COX-I/COX-2 (a manera de ejemplo solamente, piroxicam, diclofenaco, ácidos propiónicos, tales como naproxeno, flubiprofeno, fenoprofeno, quetoprofeno e ibuprofeno, fenamatos tal como ácido mefenámico, indometacina, sulindaco, azapropazona, pirazolonas tales como fenil-butazona, salicilatos tales como aspirina), inhibidores de Cox-2 (a manera de ejemplo solamente, meloxicam, celecoxib, rofecoxib, valdecoxib, lumiracoxib, parecoxib y etoricoxib); glucocorticosteroides; metotrexato, leflunomida; hidroxi-cloroquina, d-penicilamina, auranofina u otras preparaciones de oro parenterales u orales.

Los agentes quimioterapéuticos u otros agentes anti-

proliferativos utilizados en combinación con los compuestos proporcionados en la presente para tratar enfermedades proliferativas y cáncer incluyen, pero no se limitan a, cirugía, radioterapia (radiación-γ, radioterapia de haz de neutrones, radioterapia de haz de electrones, terapia de protones, braquiterapia, e isótopos radioactivos sistémicos), terapia endocrina, modificadores de la respuesta biológica (interferones, interleucinas, y factor de necrosis tumoral (TNF)), hipertermia y crioterapia, agentes para atenuar cualesquiera efectos adversos (por ejemplo, antieméticos), y otros fármacos quimioterapéuticos, incluyendo, pero no limitándose a, antraciclinas, sulfonatos de alquilo, aziridinas, etileniminas, metilmelaminas, mostazas de nitrógeno, nitrosoureas, análogos del ácido fólico, inhibidor de reductasa de dihidrofolato, análogos de purina, análogos de pirimidina, podofilotoxinas, agentes que contienen platino, interferones, interleucinas, agentes alquilantes (mecloretamina, clorambucil, Ciclofosfamida, Melfalano, Ifosfamida), anti-metabolitos (Metotrexato, gemcitabina o capecitabina), antagonistas de purina y antagonistas de pirimidina (6-Mercaptopurina, 5-fluoro-uracilo, Citarabina, Gemcitabina), venenos de huso / agentes activos en microtúbulos (Vinblastina, Vincristina, Vinorelbina, Paclitaxel, epotilona), inhibidores de topoisomerasa I, inhibidores de topoisomerasa II, podofilotoxinas (Etoposida, Irinotecano, Topotecano), antibióticos (Doxorrubicina, Bleomicina, Mitomicina), nitrosoureas (Carmustina, Lomustina), iones inorgánicos (Cisplatina, Carboplatina), enzimas (Asparaginasa), y hormonas

(Tamoxifeno, Leuprolida, Flutamida, y Megestrol), GLEEVEC^{MR}, adriamicina, dexametasona, ciclofosfamida, busulfano, improsulfano, piposulfano, benzodepa, carbocuona, meturedepa, uredepa, altretamina, trietilen-melamina, trietilen-fosforamida, trietilen-tiofosforamida, trimetilol-melamina, clorambucil, clornafazina, ciclofosfamida, estramustina, ifosfamida, mecloretamina, clorhidrato de óxido de mecloretamina, melfalano, novembiquina, fenesterina, prednimustina, trofosfamida, mostaza de uracilo, carmustina, clorozotocina, fotemustina, lomustina, nimustina, ranimustina, dacarbazina, manomustina, mitobronitol, mitolactol, pipobromano, aclacinomicinas, actinomicina F(1), antramicina, azaserina, bleomicina, cactinomicina, carubicina, carzinofilina, cromomicina, dactinomicina, daunorrubicina, daunomicina, 6-diazo-5-oxo-1-norleucina, doxorrubicina, epirrubicina, mitomicina C, ácido micofenólico, nogalamicina, olivomicina, peplomicina, plicamicina, porfiromicina, puromicina, estreptonigrina, estreptozocina, tubercidina, ubenimex, zinostatina, zorubicina, denopterina, metotrexato, pteropterina, trimetrexato, fludarabina, 6-mercaptopurina, tiamiprina, tioguanina, ancitabina, azacitidina, 6-azauridina, carmofur, citarabina, didesoxiuridina, doxifluridina, enocitabina, floxuridina, fluoro-uracilo, tegafur, L-asparaginasa, pulmozima, aceglatona, glicósido de aldofosfamida, ácido aminolevulínico, amsacrina, bestrabucil, bisantreno, carboplatina, cisplatina, defofamida, demecolcina, diazicuona, elfornitina, acetato de eliptinio, etoglucida, etoposida, flutamida, nitrato de galio,

hidroxiurea, interferón-alfa, interferón-beta, interferón-gamma, interleucina-2, lentinano, lonidamina, metotrexato, mitoguazona, mitoxantrona, mopidamol, nitracrina, pentostatina, fenamet, pirarrubicina, ácido podofilínico, 2-etil-hidrazida, procarbazina, razoxano, sizofirano, espiro-germanio, paclitaxel, tamoxifeno, teniposida, ácido tenuazónico, triazicuona, o combinaciones de los mismos.

Otros agentes utilizados en combinación con los compuestos proporcionados en la presente incluyen, pero no se limitan a: tratamientos para la enfermedad de Alzheimer, tales como ARRICEPT^{MR} y EXCELON^{MR}; tratamientos para la enfermedad de Parkinson, tales como L-DOPA/carbidopa, entacapona, ropinirol, pramipexol, bromocriptina, pergolida, trihexefendilo, y amantadina; agentes para el tratamiento de esclerosis múltiple (MS), tales como interferón beta (por ejemplo, AVONEX^{MR} y REBIF^{MR}), COPAXONE^{MR}, y mitoxantrona; tratamientos para asma, tales como albuterol y SINGULAIR^{MR}; agentes para el tratamiento de esquizofrenia, tales como ziprexa, risperdal, seroquel, y haloperidol; agentes anti-inflamatorios, tales como corticosteroides, bloqueadores de TNF, IL-1 RA, azatioprina, ciclofosfamida, y sulfasalazina; agentes inmunomoduladores e inmunosupresores, tales como ciclosporina, tacrolimus, rapamicina, micofenolato-mofetil, interferones, corticosteroides, ciclofosfamida, azatioprina, y sulfasalazina; factores neurotróficos, tales como inhibidores de acetil-colinesterasa, inhibidores de MAO, interferones, anti-

convulsionantes, bloqueadores del canal de iones, riluzol, y agentes anti-Parkinsonianos; agentes para el tratamiento de enfermedad cardiovascular, tales como bloqueadores beta, inhibidores de la enzima convertidora de angiotensina, diuréticos, nitratos, bloqueadores del canal de calcio, y estatinas; agentes para el tratamiento de enfermedad de hígado, tales como corticosteroides, colestiramina, interferones, y agentes anti-virales; agentes para el tratamiento de trastornos de la sangre, tales como corticosteroides, agentes anti-leucémicos, y factores de crecimiento; y agentes para el tratamiento de trastornos de inmunodeficiencia, tales como gamma-globulina.

En otras modalidades, los compuestos de la fórmula (I) proporcionados en la presente se utilizan como adjuntos o adyuvantes para otra terapia, por ejemplo, una terapia que utilice un inhibidor de la resorción ósea, por ejemplo, como en la terapia de osteoporosis, en particular una terapia que emplee calcio, una calcitonina o un análogo o derivado de la misma, por ejemplo, calcitonina de salmón, de anguila, o humana, una hormona esteroidea, por ejemplo, un estrógeno, un agonista parcial de estrógeno o una combinación de estrógeno-gestágeno, un SERM (Modulador Selectivo de los Receptores de Estrógeno), por ejemplo, raloxifeno, lasofoxifeno, TSE-424, FC1271, Tibolona (Livial A), vitamina D o un análogo de la misma o PTH, un fragmento de PTH o un derivado de PTH, por ejemplo, PTH (1-84), PTH (1-34), PTH (1-36), PTH (1-38), PTH (1-31)NH_2 o PTS 893.

256

Tratamiento de las enfermedades mediadas por la actividad de cinasa

Los compuestos de la fórmula (I), las sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, las composiciones farmacéuticas, y las terapias de combinación proporcionados en la presente son moduladores de la actividad de cinasa de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y ALK, y se utilizan en el tratamiento y/o la prevención de enfermedades y/o trastornos en donde una actividad aberrante, anormal o mal regulada de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK contribuye a la patología y/o sintomatología de estas enfermedades y/o trastornos. Estas enfermedades y/o trastornos mediados por las cinasas Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK se proporcionan en la presente.

En ciertas modalidades, los compuestos de la fórmula (I), las sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, las composiciones farmacéuticas, y las terapias de combinación proporcionados en la presente son inhibidores de la actividad de cinasa de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y ALK, y se utilizan en el

tratamiento y/o la prevención de las enfermedades y/o los trastornos en donde una actividad aberrante, anormal o mal regulada de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK contribuya a la patología y/o sintomatología de estas enfermedades y/o trastornos. Estas enfermedades y/o trastornos mediados por las cinasas Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK se proporcionan en la presente.

En ciertas modalidades, estas enfermedades y/o trastornos asociados con una actividad aberrante, anormal o mal regulada de las cinasas Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK incluyen, pero no se limitan a, cáncer, enfermedades proliferativas, dolor, enfermedades y/o trastornos dermatológicos, enfermedades y/o trastornos metabólicos, enfermedades y/o trastornos musculares, enfermedades y/o trastornos neurodegenerativos, enfermedades y/o trastornos neurológicos, enfermedades y/o trastornos de inmunodeficiencia, enfermedades y/o trastornos inmunológicamente mediados, enfermedades autoinmunes, enfermedades auto-inmunológicamente mediadas, enfermedades y/o trastornos óseos, enfermedades inflamatorias, fibrosis, enfermedades y/o trastornos oftálmicos/oculares, enfermedades infecciosas, enfermedades virales, reparación de heridas, enfermedades y/o trastornos respiratorios, enfermedades y/o trastornos pulmonares, enfermedad

renal, enfermedad del riñón, enfermedad hepática, enfermedades y/o trastornos cardiovasculares, enfermedades y/o trastornos vasculares, enfermedad cardíaca, muerte celular, e hiperplasia.

Las enfermedades de cáncer y proliferativas incluyen, pero no se limitan a, trastornos hematopoiéticos, malignidades hematopoiéticas, malignidades no hematopoiéticas, tumores benignos o malignos, tumores de cuello y cabeza, cáncer de cerebro, cáncer de riñón, cáncer de hígado, cáncer de glándula suprarrenal, cáncer neuronal, neuroblastoma, cáncer de vejiga, cáncer de mama, carcinoma secretor de mama, cáncer de estómago, tumores gástricos, cáncer de ovario, cáncer uterino, cáncer de colon, cáncer rectal, adenoma colo-rectal, cáncer de próstata, cáncer renal, cáncer de cerebro, cáncer endometrial, cáncer pancreático, cáncer de pulmón, cáncer pulmonar no microcelular, carcinoma quístico adenoideo humano, cáncer vaginal, cáncer de tiroides, carcinoma papilar de tiroides, sarcoma, fibrosarcoma congénito, sarcoma osteolítico, osteosarcoma, fibrosarcoma, mieloma, metástasis tumoral ósea, nefroma mesoblástico congénito, glioblastomas, melanoma, mieloma múltiple, cáncer gastrointestinal, tumores estromales gastrointestinales (GIST), mastocitosis, neuroblastoma, cánceres fibróticos, crecimiento de metástasis tumoral, hiperproliferación epidérmica, soriasis, metástasis, hiperplasia de próstata, neoplasia, neoplasia de carácter epitelial, linfomas, linfoma grande y difuso de células-B, linfoma de células-B, carcinoma mamario, tumor de Wilm, síndrome de Cowden, enfermedad de

Lhermitte-Dudos, y síndrome de Bannayan-Zonana.

Los trastornos hematopoiéticos incluyen, pero no se limitan a, trastornos mieloproliferativos, trombocitemia, trombocitosis esencial (ET), metaplasia mieloide angiogénica, mielofibrosis (MF), mielofibrosis con metaplasia mieloide (MMM), mielofibrosis idiopática crónica (IMF), policitemia vera (PV), las citopenias, y síndromes mielodisplásicos pre-malignos.

Las malignidades hematológicas incluyen, pero no se limitan a, leucemias, leucemias mieloides, leucemia de células pilosas, linfomas (linfoma no de Hodgkin), enfermedad de Hodgkin (también denominada como linfoma de Hodgkin), y mieloma, incluyendo, pero no limitándose a, leucemia linfocítica aguda (ALL), leucemia mieloide aguda (AML), leucemia pro-mielocítica aguda (APL), leucemia linfocítica crónica (CLL), leucemia mieloide crónica (CML), leucemia neutrofílica crónica (CNL), leucemia no diferenciada aguda (AUL), linfoma macrocelular anaplásico (ALCL), leucemia pro-linfocítica (PML), leucemia mielomonocítica juvenil (JMML), leucemia linfocítica aguda de células-T de adultos, leucemia mieloide aguda con mielodisplasia de tri-linaje (AML/TMDS), leucemia de linaje mixto (MLL), síndromes mielodisplásicos (MDSs), trastornos mielo-proliferativos (MPD), mieloma múltiple, (MM), sarcoma mieloide, y leucemia pro-mielocítica aguda (APL).

Los trastornos de dolor incluyen, pero no se limitan a, dolor relacionado con cáncer, dolor esquelético causado por metástasis tumoral, osteoartritis, dolor visceral, dolor inflamatorio, y dolor

neurogénico.

Las enfermedades y/o los trastornos dermatológicos incluyen, pero no se limitan a, condiciones inflamatorias o alérgicas de la piel, dermatitis, eczema, soriasis, dermatitis atópica, dermatitis seborreica (caspa, costra láctea), irritación por el pañal, dermatitis por contacto inducida por urushiol, dermatitis por contacto, eritrodermia, liquen simple crónico, prurigo nodular, comezón, prurito anal, dermatitis numular, dishidrosis, pitiriasis alba, alopecia areata, eritema multiforme, dermatitis herpetiforme, esclerodermia, vitiligo, angiitis por hipersensibilidad, urticaria, penfigoide bulloso, lupus eritematoso, pénfigo, epidermólisis bullosa adquirida, adhesión peritoneal y subdérmica, y fotoenvejecimiento de la piel.

Las enfermedades y/o los trastornos metabólicos y los trastornos en el comer incluyen, pero no se limitan a, obesidad, diabetes, y anorexia.

Las enfermedades y/o los trastornos musculares incluyen, pero no se limitan a, atrofias musculares (por ejemplo, desuso), distrofias musculares (por ejemplo, distrofia muscular de Duchenne, distrofia muscular de Becker, distrofia muscular de la cintura escapulohumeral o pélvica), sarcopenia, caquexia, consunción, y distrofia facioescapulohumeral.

Las enfermedades y/o los trastornos neurológicos y los trastornos neurodegenerativos incluyen, pero no se limitan a, función neurológica deteriorada y enfermedad de Alzheimer.

Las enfermedades y/o los trastornos de inmunodeficiencia las

enfermedades y/o los trastornos inmunológicamente mediados incluyen, pero no se limitan a, condiciones inmunológicas patológicas que involucran activación de las células-T, anafilaxis, alergia, y soriasis. Los trastornos de alergia incluyen, pero no se limitan a, enfermedades respiratorias y trastornos dermatológicos.

Los trastornos inmunológicamente mediados incluyen, pero no se limitan a, alergia y soriasis. Los trastornos de alergia incluyen, pero no se limitan a, enfermedades respiratorias y trastornos dermatológicos.

Las enfermedades y/o los trastornos autoinmunes y las enfermedades y/o los trastornos auto-inmunológicamente mediados incluyen, pero no se limitan a, artritis destructiva, artritis reumatoide, lupus eritematoso sistémico, síndrome de Sjogren, esclerosis múltiple, dermatomiositis, esclerosis sistémica progresiva, enfermedades que afecten a la nariz, incluyendo rinitis alérgica, y enfermedad inflamatoria en donde estén implicadas reacciones autoinmunes o que tenga un componente o etiología autoinmune, incluyendo trastornos hematológicos autoinmunes (por ejemplo, anemia hemolítica, anemia aplásica, anemia de glóbulos rojos puros, púrpura trombocitopénica idiopática y trombocitopenia idiopática), cirrosis biliar primaria (PBC), lupus, lupus eritematoso sistémico, policondritis, esclerodoma, granulomatosis de Wegener, dermatomiositis, hepatitis activa crónica, miastenia grave, síndrome de Steven-Johnson, prurito idiopático, enfermedad inflamatoria autoinmune del intestino (por ejemplo, colitis ulcerativa y enfermedad

de Crohn), oftalmopatía endocrina, enfermedad de Graves, sarcoidosis, alveolitis, neumonitis de hipersensibilidad crónica, esclerosis múltiple, cirrosis biliar primaria, uveítis (anterior y posterior), queratoconjuntivitis sicca y queratoconjuntivitis vernal, fibrosis pulmonar intersticial, artritis soriática, y glomerulonefritis (con y sin síndrome nefrótico, por ejemplo, incluyendo síndrome nefrótico idiopático o nefropatía de cambio mínimo).

Las enfermedades y/o los trastornos óseos incluyen, pero no se limitan a, osteoporosis, osteítis deformante, enfermedad de Paget, osteoartritis, falla de prótesis, osteopenia, y fracturas y otros trastornos en donde una baja densidad mineral ósea sea un signo de la enfermedad.

Las enfermedades y/o los trastornos inflamatorios incluyen, pero no se limitan a, uveítis, ateroesclerosis, aterogénesis, glomerulonefritis, enfermedad de Kawasaki, respuestas inflamatorias, polimiositis, artritis, inflamación neurológica, inflamación por artritis crónica, y osteoartritis.

Las enfermedades y/o los trastornos de fibrosis incluyen, pero no se limitan a, acumulación de matriz extracelular y fibrosis, esclerodermia, fibroesclerosis, fibrosis inducida por radiación, fibrosis del riñón, fibrosis pulmonar y fibrosis hepática, hemocromatosis, cirrosis biliar primaria, restenosis, fibrosis retroperitoneal, fibrosis mesentérica, endometriosis, y queloides.

Las enfermedades y/o los trastornos oftálmicos/oculares incluyen, pero no se limitan a, vítreo-retinopatía proliferativa,

escarificación ocular, escarificación de córnea, trastornos oculares, heridas de córnea, conjuntivitis, queratoconjuntivitis sicca, y conjuntivitis vernal.

Las infecciones y las enfermedades y/o los trastornos virales incluyen, pero no se limitan a, infección por VIH-1, por ejemplo, virus de hepatitis B (HBV), virus de hepatitis C (HCV), hepatitis inducida por alcohol.

La reparación de heridas incluye, pero no se limita a, formación excesiva o hipertrófica de escara o queloide en la dermis que se presente durante el sanado de heridas resultantes de trauma, o de heridas quirúrgicas, úlceras (incluyendo úlceras diabéticas, úlceras crónicas, úlceras gástricas, y úlceras duodenales).

Las enfermedades y/o los trastornos respiratorios y los trastornos pulmonares incluyen, pero no se limitan a, asma, asma bronquial, asma alérgico, asma intrínseco (no alérgico), asma extrínseco (alérgico), asma inducido por ejercicio, asma inducido por fármacos (incluyendo inducido por aspirina y por fármacos anti-inflamatorios no esteroideos (NSAID)), y asma inducido por polvo, enfermedad pulmonar obstructiva crónica (COPD); enfermedad obstructiva crónica de las vías respiratorias (COAD), enfermedad obstructiva crónica del pulmón (COLD), bronquitis, bronquitis crónica, bronquitis aguda, disnea, bronquitis araquídica, bronquitis catarral, bronquitis cruposa, bronquitis ftinoide, rinitis, rinitis aguda, rinitis crónica, rinitis medicamentosa, rinitis vasomotora, rinitis alérgica perenne y de temporada, rinitis nerviosa (fiebre de heno),

enfermedades inflamatorias u obstructivas de las vías respiratorias, hipertensión pulmonar, lesión pulmonar aguda, síndrome de insuficiencia respiratoria de adultos/aguda (ARDS), fibrosis pulmonar, fibrosis pulmonar idiopática, enfermedad pulmonar obstructiva crónica, enfermedad pulmonar debida a agentes infecciosos o tóxicos, enfisema, neumoconiosis, aluminosis, antracosis, asbestosis, calicosis, ptilosis, siderosis, silicosis, tabacosis, bisinosis, lesión pulmonar aguda (ALI), hipereosinofilia, síndrome de Löffler, neumonía eosinofílica, infestación parasitaria (en particular de metazoarios) (incluyendo eosinofilia tropical), aspergilosis broncopulmonar, poliarteritis nodosa (incluyendo síndrome de Churg-Strauss), granuloma eosinofílico, trastornos relacionados con los eosinófilos que afecten a las vías respiratorias, ocasionados por reacción a fármacos, hipertensión pulmonar, hipertensión pulmonar primaria (PPH), hipertensión pulmonar secundaria (SPH), hipertensión pulmonar primaria familiar, hipertensión pulmonar primaria esporádica, hipertensión pulmonar pre-capilar, hipertensión arterial pulmonar (PAH), hipertensión de arteria pulmonar, hipertensión pulmonar idiopática, arteriopatía pulmonar trombótica (TPA), arteriopatía pulmonar plexogénica, arteriopatía pulmonar funcional clases I a IV, e hipertensión pulmonar asociada con, relacionada con, o secundaria a, disfunción de ventrículo izquierdo, enfermedad de válvula mitral, pericarditis constrictiva, estenosis aórtica, cardiomiopatía, fibrosis mediastinal, drenaje venoso pulmonar anómalo, enfermedad oclusiva venosa

pulmonar, enfermedad vascular de colágeno, enfermedad cardíaca congénita, infección por virus VIH, fármacos y toxinas, tales como fenfluraminas, hipoxemia, hipertensión venosa pulmonar, enfermedad pulmonar obstructiva crónica, enfermedad intersticial pulmonar, respiración trastornada en el sueño, trastorno de hipoventilación alveolar, exposición crónica a alta altitud, enfermedad pulmonar neonatal, displasia capilar alveolar, enfermedad drepanocítica, otro trastorno de la coagulación, tromboémbolos crónicos, enfermedad del tejido conectivo, lupus, esquistosomiasis, sarcoidosis, o hemangiomatosis capilar pulmonar.

Las enfermedades y/o los trastornos renales incluyen, pero no se limitan a, glomerulonefritis, fibrosis intersticial renal, fibrosis renal, enfermedad renal crónica y enfermedad renal aguda. Las enfermedades y/o los trastornos del riñón incluyen, pero no se limitan a, nefropatía diabética, nefritis por lupus, nefropatía inducida por hipertensión, nefropatía asociada con VIH y necropatía de trasplante. Las enfermedades y/o los trastornos del hígado incluyen, pero no se limitan a, disfunción hepática atribuible a infecciones, hepatitis inducida por alcohol, trastornos del árbol biliar, e isquemia hepática.

Las enfermedades y/o los trastornos cardiovasculares, vasculares, o cardíacos incluyen, pero no se limitan a, insuficiencia cardíaca congestiva, fibrosis cardíaca posterior a infarto, insuficiencia cardíaca congestiva, reperfusión/isquemia en embolia, ataques al corazón, e hipoxia de órganos, isquemia, cardiomiopatía

261

dilatada, miocarditis, infarto de miocardio, estenosis vascular, restenosis, ateroesclerosis, disfunción eréctil masculina, síndrome de Raynaud, trombosis, y acumulación de plaquetas inducida por trombina.

En otras modalidades, los compuestos de la fórmula (I) proporcionados en la presente son agentes inmunosupresores, y se utilizan para tratar rechazo de trasplante de órgano, rechazo crónico de trasplante, lupus, esclerosis múltiple, artritis reumatoide, soriasis, dermatitis, enfermedad de Crohn, diabetes tipo-1 y complicaciones de diabetes tipo-1.

En ciertas modalidades, los compuestos de la fórmula (I), las sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, las composiciones farmacéuticas, y/o las combinaciones proporcionadas en la presente, se utilizan en el tratamiento y/o la prevención de las enfermedades y/o los trastornos respiratorios incluyendo, pero no limitándose a, asma, asma bronquial, asma alérgico, asma intrínseco, asma extrínseco, asma inducido por ejercicio, asma inducido por fármacos (incluyendo inducido por aspirina y por fármacos anti-inflamatorios no esteroideos (NSAID)), y asma inducido por polvo, enfermedad pulmonar obstructiva crónica (COPD); bronquitis, rinitis aguda y crónica, incluyendo rinitis medicamentosa, y rinitis vasomotora; rinitis alérgica perenne y de temporada, incluyendo rinitis nerviosa (fiebre de heno).

En ciertas modalidades, los compuestos de la fórmula (I), las

sales farmacéuticamente aceptables, solvatos, N-óxidos, profármacos e isómeros de los mismos, las composiciones farmacéuticas, y/o las combinaciones proporcionadas en la presente, se utilizan en el tratamiento y/o la prevención de trastornos dermatológicos, incluyendo, pero no limitándose a, soriasis, dermatitis, eczema, dermatitis atópica, dermatitis por contacto, dermatitis por contacto inducida por urushiol, dermatosis eczematosas, y reacciones de hipersensibilidad de tipo retardado; fito- y foto-dermatitis; dermatitis seborreica, dermatitis herpetiforme, liquen simple crónico, liquen plano, liquen escleroso y atrófico, lupus eritematoso discoide, irritación por el pañal, eritrodermia, prurigo nodular, comezón, prurito anal, dermatitis numular, dishidrosis, y pitiriasis alba.

En ciertas modalidades, los compuestos de la fórmula (I), las sales farmacéuticamente aceptables, solvatos, N-óxidos, profármacos e isómeros de los mismos, las composiciones farmacéuticas, y/o las combinaciones proporcionadas en la presente, se utilizan en el tratamiento y/o la prevención de cáncer, incluyendo, pero no limitándose a, trastornos hematopoiéticos, malignidades hematopoiéticas, malignidades no hematopoiéticas, tumores benignos o malignos, tumores de cuello y cabeza, cáncer de cerebro, cáncer de riñón, cáncer de hígado, cáncer de glándula suprarrenal, cáncer neuronal, neuroblastoma, cáncer de vejiga, cáncer de mama, carcinoma secretor de mama, cáncer de estómago, tumores gástricos, cáncer de ovario, cáncer uterino, cáncer de colon, cáncer

rectal, adenoma colo-rectal, cáncer de próstata, cáncer renal, cáncer de cerebro, cáncer endometrial, cáncer pancreático, cáncer de pulmón, cáncer pulmonar no microcelular, carcinoma quístico adenoideo humano, cáncer vaginal, cáncer de tiroides, carcinoma papilar de tiroides, sarcoma, fibrosarcoma congénito, sarcoma osteolítico, osteosarcoma, fibrosarcoma, mieloma, metástasis tumoral ósea, nefroma mesoblástico congénito, glioblastomas, melanoma, mieloma múltiple, cáncer gastrointestinal, tumores estromales gastrointestinales (GIST), mastocitosis, neuroblastoma, cánceres fibróticos, crecimiento de metástasis tumoral, hiperproliferación epidérmica, soriasis, metástasis, hiperplasia de próstata, neoplasia, neoplasia de carácter epitelial, linfomas, linfoma grande y difuso de células-B, linfoma de células-B, carcinoma mamario, tumor de Wilm, síndrome de Cowden, enfermedad de Lhermitte-Dudos, y síndrome de Bannayan-Zonana.

En ciertas modalidades, los compuestos de la fórmula (I), las sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, las composiciones farmacéuticas, y/o las combinaciones proporcionadas en la presente, se utilizan en el tratamiento y/o la prevención de cáncer, incluyendo, pero no limitándose a, trastornos hematopoiéticos, malignidades hematopoiéticas, malignidades no hematopoiéticas, tumores benignos o malignos, tumores de cuello y cabeza, cáncer de cerebro, cáncer de riñón, cáncer de hígado, cáncer de glándula suprarrenal, cáncer neuronal, neuroblastoma, cáncer de vejiga, cáncer de mama,

carcinoma secretor de mama, cáncer de estómago, tumores gástricos, cáncer de ovario, cáncer uterino, cáncer de colon, cáncer rectal, adenoma colo-rectal, cáncer de próstata, cáncer renal, cáncer de cerebro, cáncer endometrial, cáncer pancreático, cáncer de pulmón, cáncer pulmonar no microcelular, carcinoma quístico adenoideo humano, cáncer vaginal, cáncer de tiroides, carcinoma papilar de tiroides, sarcoma, fibrosarcoma congénito, sarcoma osteolítico, osteosarcoma, fibrosarcoma, mieloma, metástasis tumoral ósea, nefroma mesoblástico congénito, glioblastomas, melanoma, mieloma múltiple, cáncer gastrointestinal, tumores estromales gastrointestinales (GIST), mastocitosis, neuroblastoma, cánceres fibróticos, crecimiento de metástasis tumoral, hiperproliferación epidérmica, soriasis, metástasis, hiperplasia de próstata, neoplasia, neoplasia de carácter epitelial, linfomas, linfoma grande y difuso de células-B, linfoma de células-B, carcinoma mamario, tumor de Wilm, síndrome de Cowden, enfermedad de Lhermitte-Dudos, y síndrome de Bannayan-Zonana. Los trastornos hematopoiéticos incluyen, pero no se limitan a, trastornos mieloproliferativos, trombocitemia, trombocitosis esencial (ET), metaplasia mieloide angiogénica, mielofibrosis (MF), mielofibrosis con metaplasia mieloide (MMM), mielofibrosis idiopática crónica (IMF), policitemia vera (PV), las citopenias, y síndromes mielodisplásicos pre-malignos. Las malignidades hematológicas incluyen, pero no se limitan a, leucemias, leucemias mieloides, leucemia de células pilosas, linfomas (linfoma no de Hodgkin),

enfermedad de Hodgkin (también denominada como linfoma de Hodgkin), y mieloma, incluyendo, pero no limitándose a, leucemia linfocítica aguda (ALL), leucemia mieloide aguda (AML), leucemia pro-mielocítica aguda (APL), leucemia linfocítica crónica (CLL), leucemia mieloide crónica (CML), leucemia neutrofílica crónica (CNL), leucemia no diferenciada aguda (AUL), linfoma macrocelular anaplásico (ALCL), leucemia pro-linfocítica (PML), leucemia mielomonocítica juvenil (JMML), leucemia linfocítica aguda de células-T de adultos, leucemia mieloide aguda con mielodisplasia de tri-linaje (AML/TMDS), leucemia de linaje mixto (MLL), síndromes mielodisplásicos (MDSs), trastornos mieloproliferativos (MPD), mieloma múltiple, (MM), sarcoma mieloide, y leucemia pro-mielocítica aguda (APL).

En ciertas modalidades, los compuestos de la fórmula (I), las sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, y las composiciones farmacéuticas y las terapias de combinación proporcionadas en la presente, se utilizan como agentes inmunosupresores para tratar y/o prevenir artritis reumatoide (RA), esclerosis múltiple (MS), lupus eritematoso sistémico (SLE), púrpura tromocitopénica inmune (ITP), anemia hemolítica, y rechazo de trasplante.

Los compuestos de la fórmula (I), las sales farmacéuticamente aceptables, solvatos, N-óxidos, pro-fármacos e isómeros de los mismos, las composiciones farmacéuticas, y las terapias de combinación proporcionadas en la presente, se utilizan en los

métodos para modular la actividad de cinasa de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y ALK en un sujeto (humano u otro mamífero) para el tratamiento y/o la prevención de las enfermedades y/o los trastornos asociados con, o mediados por, una actividad aberrante, anormal, o mal regulada de cinasa Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK. En ciertas modalidades, estos métodos incluyen administrar a un sujeto una cantidad efectiva de un compuesto de la fórmula (I), o una composición farmacéutica que contenga un compuesto de la fórmula (I).

En ciertas modalidades, los métodos para el tratamiento de un sujeto que sufra de una enfermedad y/o trastorno asociado con una actividad aberrante, anormal, o mal regulada de cinasa Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK, incluyen administrar al sujeto una cantidad efectiva de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable o un solvato del mismo, ya sea solo o bien como parte de una composición farmacéutica, como se describe en la presente.

En ciertas modalidades, un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable o un solvato del mismo, se utiliza en la preparación de un medicamento para el tratamiento de una enfermedad o trastorno asociado con una actividad aberrante, anormal, o mal regulada de cinasa Ros, KDR, FMS, c-FMS, FLT3, c-

Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK. En otras modalidades, un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable o un solvato del mismo, se utiliza en el tratamiento de una enfermedad o trastorno asociado con una actividad aberrante, anormal, o mal regulada de cinasa Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK.

En una modalidad adicional, las composiciones farmacéuticas que comprenden cuando menos un compuesto de la fórmula (I) se adaptan para su administración oral, para el tratamiento de una enfermedad o trastorno asociado con una actividad aberrante, anormal, o mal regulada de cinasa Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK. En una modalidad adicional, las composiciones farmacéuticas que comprenden cuando menos un compuesto de la fórmula (I) se adaptan para su administración tópica, para el tratamiento de una enfermedad o trastorno asociado con una actividad aberrante, anormal, o mal regulada de cinasa Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK. En una modalidad adicional, las composiciones farmacéuticas que comprenden cuando menos un compuesto de la fórmula (I) se adaptan para su administración parenteral, para el tratamiento de una enfermedad o trastorno asociado con una actividad aberrante, anormal, o mal regulada de cinasa Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3,

Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK. En una modalidad adicional, las composiciones farmacéuticas que comprenden cuando menos un compuesto de la fórmula (I) se adaptan para su administración pulmonar/mediante inhalación, para el tratamiento de una enfermedad o trastorno asociado con una actividad aberrante, anormal, o mal regulada de cinasa Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK.

En ciertas modalidades, el sistema o sujeto utilizado en los métodos proporcionados en la presente es una célula o un sistema de tejidos. En ciertas modalidades, el sistema o sujeto utilizado en los métodos proporcionados en la presente es un sujeto humano o animal.

De acuerdo con lo anterior, en la presente se proporcionan métodos para prevenir, tratar y/o mitigar una condición de cualquiera de las enfermedades o trastornos descritos anteriormente, en un sujeto que necesite dicho tratamiento, cuyo método comprende administrar a este sujeto, una cantidad terapéuticamente efectiva de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo. Para cualquiera de los métodos y usos proporcionados en la presente, la dosificación requerida variará dependiendo del modo de administración, de la condición particular que se vaya a tratar, y del efecto deseado.

765

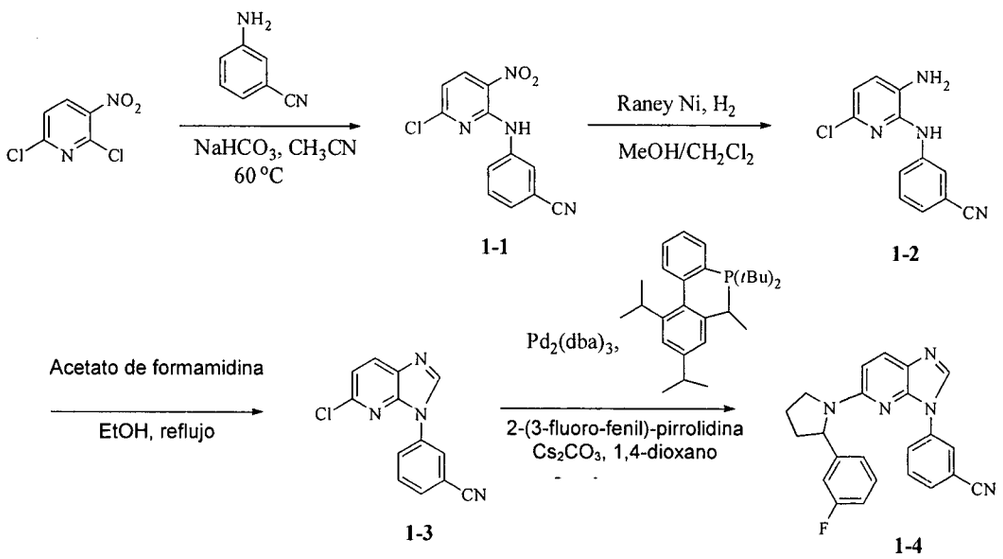
Kits

También en la presente se proporcionan paquetes farmacéuticos o kits que incluyen uno o más recipientes que contienen un compuesto de la fórmula (I) útil para el tratamiento o la prevención de una enfermedad o trastorno mediado por las cinasas Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK. En otras modalidades, estos paquetes farmacéuticos o kits incluyen uno o más recipientes que contienen un compuesto de la fórmula (I) útil para el tratamiento o la prevención de una enfermedad o trastorno mediado por las cinasas Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK, y uno o más recipientes que contienen un agente terapéutico adicional, incluyendo, pero no limitándose a, aquéllos enlistados anteriormente. En ciertas modalidades, estos paquetes farmacéuticos o kits opcionalmente incluyen instrucciones para la administración de un compuesto de la fórmula (I).

EJEMPLOS

Los siguientes ejemplos se ofrecen para ilustrar, pero no para limitar, los compuestos de la fórmula (I) proporcionados en la presente, y la preparación de estos compuestos.

Esquema 1



Ejemplo 1

Preparación de 3-(5-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3H-imidazo [4,5-b]-piridin-3-il)-benzonitrilo

El 3-(5-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo (1-4) se sintetizó en cuatro pasos como se muestra en el esquema 1.

En el paso 1-1, se agregó bicarbonato de sodio (1.68 gramos, 20 milimoles) a una solución de 2,6-dicloro-3-nitro-piridina (1.93 gramos, 10 milimoles), y 3-amino-benzonitrilo (1.18 gramos, 10 milimoles) en acetonitrilo y la suspensión se calentó durante 24 horas a 60°C. La mezcla se filtró y se lavó dos veces con agua para

dar el 3-(6-cloro-3-nitro-piridin-2-il-amino)-benzonitrilo (1-1) como un sólido amarillo pálido. ^{1}H RMN DMSO-d6 δ (ppm) 10.24 (s, 1H), 8.57 (d, 1H), 8.09 (m, 1H), 7.93 (m, 1H), 7.62 (m, 2H), 7.08 (d, 1H); *m/z* 357 M+1.

En el paso 1-2, se agregó Níquel de Raney a una suspensión de 3-(6-cloro-3-nitro-piridin-2-il-amino)-benzonitrilo en metanol/ dicloro-metano (1:1), y la suspensión resultante se estableció en un agitador Parr bajo una atmósfera de hidrógeno (2.8 kg/cm^2) durante 18 horas. El catalizador restante se removió a través de un cojín de Celite, y la mezcla de reacción se concentró, para proporcionar el producto crudo del 3-(3-amino-6-cloro-piridin-2-il-amino)-benzonitrilo (1-2), el cual se utilizó en el siguiente paso sin mayor purificación.

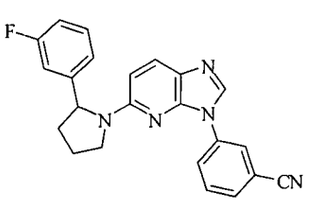
En el paso 1-3, una solución de 3-(3-amino-6-cloro-piridin-2-il-amino)-benzonitrilo (1.07 gramos, 4.38 milimoles), y acetato de formamidina (1.37 gramos, 13.1 milimoles) en etanol se puso a reflujo durante 3 horas. La mezcla de reacción se concentró y se purificó, para proporcionar el 3-(5-cloro-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo (1-3) como un sólido amarillo.

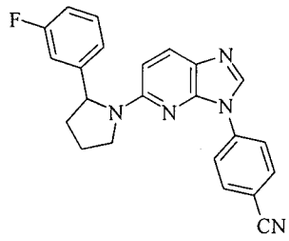
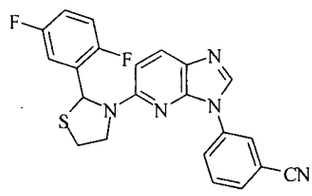
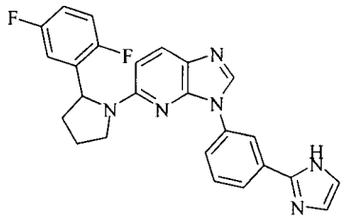
En el paso 1-4, se agregaron *tris*-(dibenciliden-acetona)-dipaladio(0) (10.8 miligramos, 0.012 milimoles), diciclohexil-(2',4',6'-tri-isopropil-bifenil-2-il)-fosfina (22 miligramos, 0.047 milimoles), y carbonato de cesio (77 miligramos, 0.24 milimoles) consecutivamente a una solución de 3-(5-cloro-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo (30 miligramos, 0.12 milimoles), y 2-(3-fluoro-fenil)-pirrolidina (29 miligramos, 0.18 milimoles) en 1,4-dioxano. La mezcla

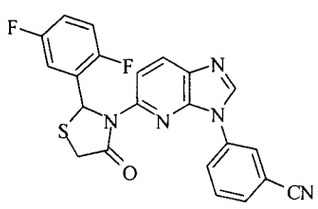
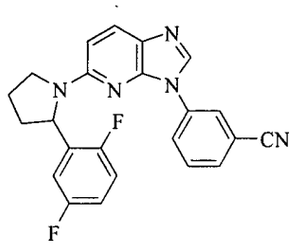
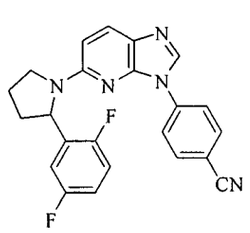
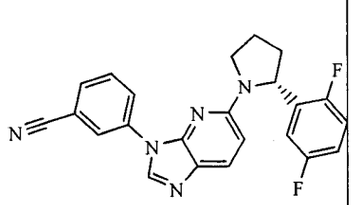
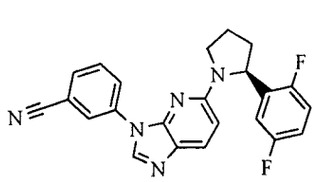
se desgasificó mediante vacío, y se cargó con nitrógeno, y se calentó durante 18 horas a 100°C. La mezcla de reacción se purificó utilizando HPLC para proporcionar el 3-(5-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo (1-4) como un sólido blanco. ^{1}H RMN metanol-d4 δ (ppm) 8.86 (s, 1H), 8.28 (s, 1H), 7.98 (m, 1H), 7.89 (d, 1H), 7.78 (d, 1H), 7.63 (t, 1H), 7.33 (m, 1H), 7.09 (dm, 1H), 6.93(m, 2H), 6.70 (d, 1H), 5.18 (d, 1H), 3.94 (m, 1H), 3.68 (m, 1H), 2.48 (m, 1H), 2.11 (m, 2), 1.97 (m, 1H); *m/z* 384 (M+1).

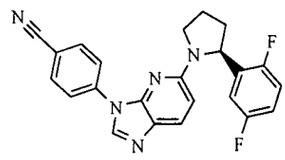
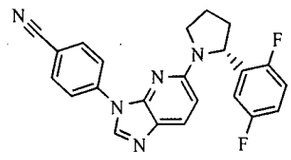
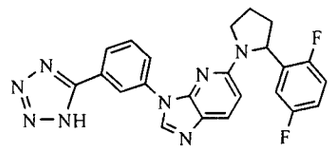
Mediante la repetición de los procedimientos descritos en los ejemplos anteriores, utilizando los materiales de partida apropiados, se obtuvieron los siguientes compuestos de la fórmula I, como se definen en la Tabla 1.

Tabla 1

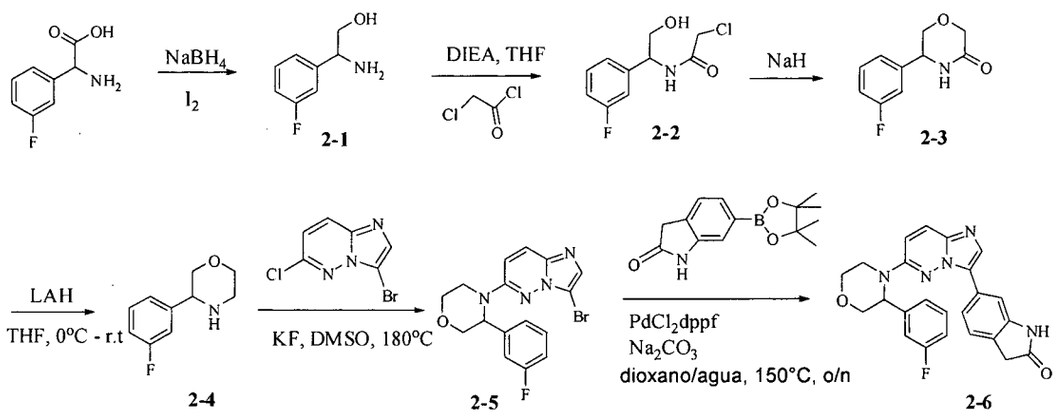
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
1		^{1}H RMN metanol-d4 δ (ppm) 8.86 (s, 1H), 8.28 (s, 1H), 7.98 (m, 1H), 7.89 (d, 1H), 7.78 (d, 1H), 7.63 (t, 1H), 7.33 (m, 1H), 7.09 (dm, 1H), 6.93(m, 2H), 6.70 (d, 1H), 5.18 (d, 1H), 3.94

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(m, 1H), 3.68 (m, 1H), 2.48 (m, 1H), 2.11 (m, 2), 1.97 (m, 1H); *m/z* 384 (M+1)
2		^{1}H RMN metanol-d4 δ (ppm) 8.79 (s, 1H), 7.89 (m, 3H), 7.80 (m, 2H), 7.36 (m, 1H), 7.09 (d, 1H), 6.99 (m, 2H), 6.70 (d, 1H), 5.13 (dd, 1H), 3.94 (m, 1H), 3.69 (m, 1H), 2.49 (m, 1H), 2.11 (m, 2H), 1.97 (m, 1H); *m/z* 384 (M+1)
3		*m/z* 420 (M+1)
4		*m/z* 443 (M+1)

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
5		*m/z* 443 (M+1)
6		MS *m/z* 402 (M+1)
7		MS *m/z* 402 (M+1)
8		MS *m/z* 402 (M+1)
9		MS *m/z* 402 (M+1)

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
10		MS *m/z* 402 (M+1)
11		MS *m/z* 402 (M+1)
12		MS *m/z* 402 (M+1)

Esquema 2



Ejemplo 2

6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-indolin-2-ona

El 3-(5-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo (1-4) se sintetizó en seis pasos como se muestra en el esquema 2.

En el paso 2-1, se agregó D,L-3-fluoro-fenil-glicina (10 gramos, 59.2 milimoles) a una suspensión de $NaBH_4$ (5.37 gramos, 142 milimoles) en tetrahidrofurano (200 mililitros). La suspensión se enfrió a 0°C, y se agregó por goteo una solución de yodo (15 gramos, 59.2 milimoles) en tetrahidrofurano,. La solución resultante se calentó mientras se agitaba durante la noche. Esta solución se enfrió a temperatura ambiente, se apagó con una solución de KOH al 20 por ciento (150 mililitros), y se extrajo con dicloro-metano (3 veces). Los orgánicos se combinaron, se secaron sobre $MgSO_4$ y el solvente se removió utilizando un evaporador giratorio. El producto se purificó mediante cromatografía por evaporación instantánea (del 0 al 10 por ciento de metanol/acetato de etilo), para proporcionar el 2-amino-2-(3-fluoro-fenil)-etanol (2-1) como un residuo blanco.

En el paso 2-2, se agregó trietil-amina (8.15 mililitros, 58.6 milimoles) en una porción individual, a una solución de 2-amino-2-(3-fluoro-fenil)-etanol (7.57 gramos, 48.8 milimoles) en tetrahidrofurano, se enfrió a 0°C y se agregó por goteo cloruro de cloro-acetilo (5.08 mililitros, 58.6 milimoles). La mezcla se enfrió a 0°C, y se agitó durante 1 hora. La mezcla de reacción se apagó con agua y la fase

orgánica se lavó con HCl 0.5 N, $NaHCO_3$ saturado, salmuera, y se secó sobre $MgSO_4$. La fase orgánica se concentró, y se purificó mediante cromatografía por evaporación instantánea (50 por ciento de EtOAc/hexanos), para proporcionar la 2-cloro-*N*-(1-(3-fluoro-fenil)-2-hidroxi-etil)-acetamida (2-2) como un sólido amarillo.

En el paso 2-3, se agregó lentamente una solución de 2-cloro-*N*-(1-(3-fluoro-fenil)-2-hidroxi-etil)-acetamida (5.5 gramos, 24 milimoles) en tetrahidrofurano (150 mililitros) a una suspensión de NaH (1.05 gramos, 26 milimoles) en tetrahidrofurano (600 mililitros) a 0°C. La solución heterogénea se calentó a temperatura ambiente, y se agitó durante la noche. La mezcla de reacción se apagó, se concentró, y se agregó acetato de etilo al residuo. Esta solución se lavó con agua y salmuera, y la fase orgánica se secó sobre $MgSO_4$, se filtra, y se concentró, para proporcionar la 5-(3-fluoro-fenil)-morfolin-3-ona (2-3).

En el paso 2-4, una solución de 5-(3-fluoro-fenil)-morfolin-3-ona (4.56 gramos, 23.4 milimoles) en tetrahidrofurano a 0°C, se trató con hidruro de litio y aluminio (4.3 gramos, 107 milimoles) en una porción individual. La suspensión se calentó a temperatura ambiente, y se agitó durante la noche. La mezcla de reacción se apagó con $Na_2SO_4 \cdot 10\ H_2O$ y se agitó durante 4 horas. La solución heterogénea se filtró a través de un cojín de Celite, y el filtrado se concentró y se purificó mediante cromatografía por evaporación instantánea (del 5 al 10 por ciento de metanol/EtOAc), para obtener la 3-(3-fluoro-fenil)-morfolina (2-4) como un aceite transparente. ^1H RMN $CDCl_3$ (δ) ppm

7.28 (m, 1H), 7.13 (m, 2H), 6.97 (m, 1H), 3.93 (dd, 1H), 3.89 (m, 1H), 3.81 (dd, 1H), 3.64 (td, 1H), 3.35 (m, 1H), 3.12 (td, 1H), 3.02 (m, 1H).

En el paso 2-5, una suspensión de 3-(3-fluoro-fenil)-morfolina (1.59 gramos, 6.9 milimoles), 3-bromo-6-cloro-imidazo-[1,2-b]-piridazina (12-1) (1.5 gramos, 8.29 milimoles), y fluoruro de potasio (1.6 gramos, 27.6 milimoles) en sulfóxido de dimetilo (6 mililitros), se calentó a 180°C durante 18 horas mientras se agitaba. La solución resultante se enfrió a temperatura ambiente, y se purificó mediante HPLC, para proporcionar la 4-(3-bromo-imidazo-[1,2-b]-piridazin-6-il)-3-(3-fluoro-fenil)-morfolina (2-5) como una espuma amarilla.

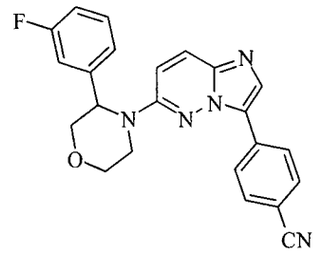
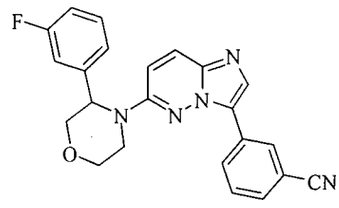
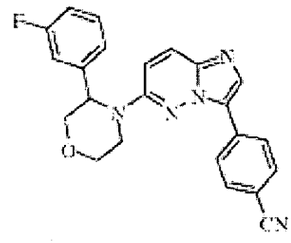
En el paso 2-6, una suspensión de 4-(3-bromo-imidazo-[1,2-b]-piridazin-6-il)-3-(3-fluoro-fenil)-morfolina (25 miligramos, 0.067 milimoles), 6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-indolin-2-ona (34 miligramos, 0.13 milimoles), y [1,1'-bis-(difenil-fosfino)-ferroceno]-dicloro-paladio(II) (2.7 miligramos, 0.0033 milimoles) en 3 mililitros de 1,4-dioxano y 0.5 mililitros de carbonato de sodio 2.0M, se burbujeó con nitrógeno y se calentó a 150°C, y se agitó durante 20 horas. La solución se enfrió a temperatura ambiente, y se purificó mediante HPLC para proporcionar la 6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-indolin-2-ona (2-6) como un sólido blanco.

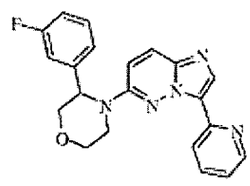
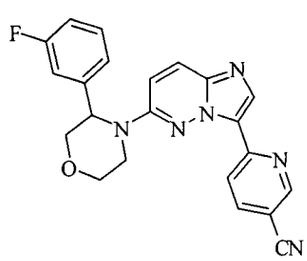
Mediante la repetición de los procedimientos descritos en los ejemplos anteriores, utilizando los materiales de partida apropiados, se obtuvieron los siguientes compuestos de la fórmula I, como se

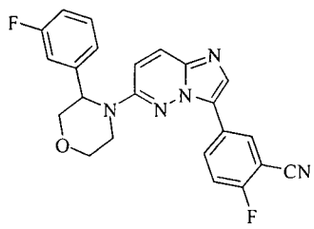
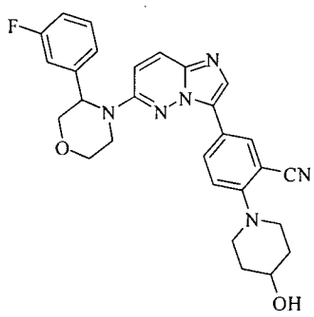
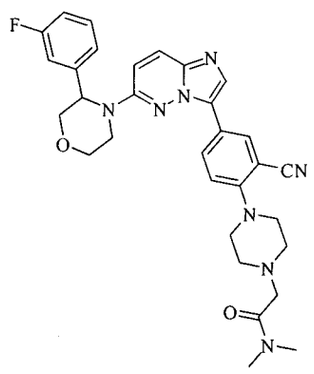
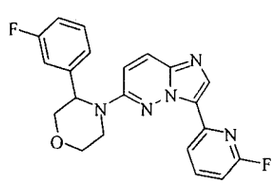
270

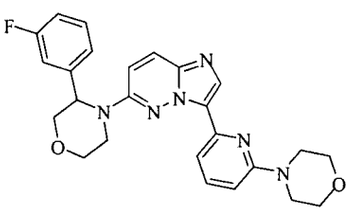
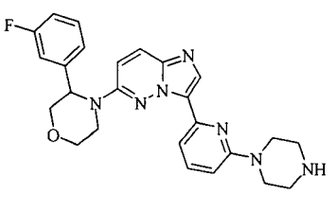
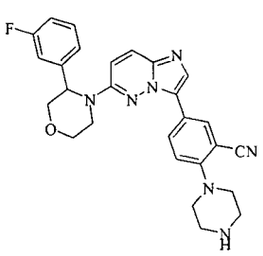
definen en la Tabla 2.

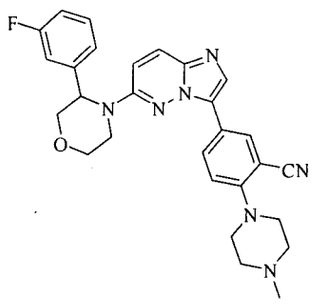
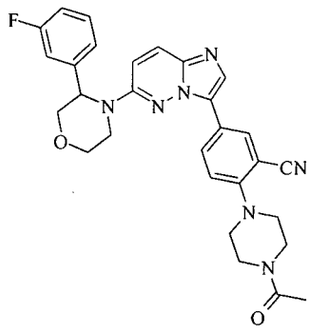
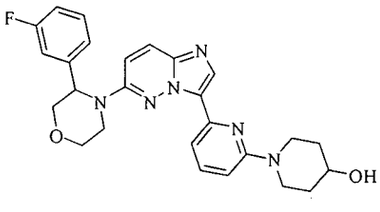
Tabla 2

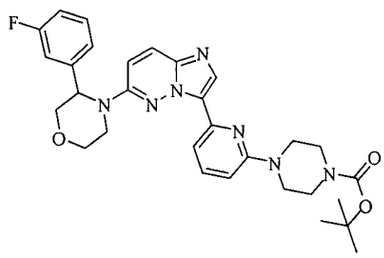
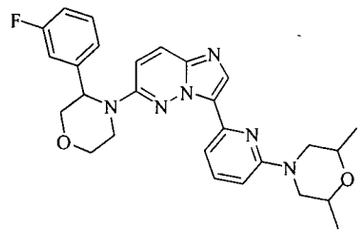
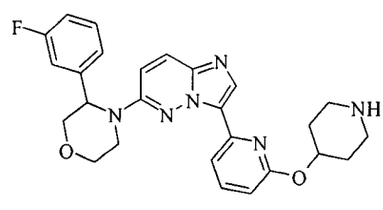
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
1		^{1}H RMN metanol-d4 δ (ppm) 7.97 (m, 3H), 7.72 (d, 2H), 7.66 (b, 1H), 7.45 (s, 1H), 2.24 (q, 1H), 7.11 (d, 1H), 7.07 (m, 1H), 6.89 (m, 1H), 5.17 (m, 1H), 1.46 (dd, 1H), 4.00 (m, 3H), 3.76 (m, 1H), 3.66 (m, 1H); *m/z* 400 (M+1)
2		*m/z* 400 (M+1)
3		^{1}H RMN metanol-d4 δ (ppm) 7.97 (m, 3H), 7.72 (d, 2H), 7.66 (b, 1H), 7.45 (s, 1H), 2.24 (q, 1H), 7.11 (d, 1H), 7.07 (m, 1H), 6.89 (m, 1H),

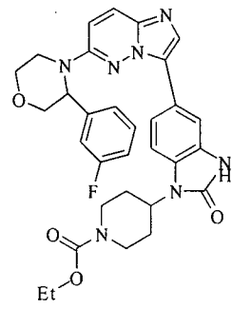
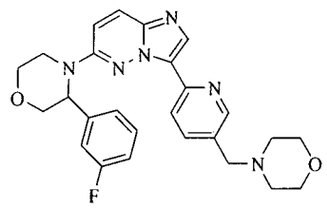
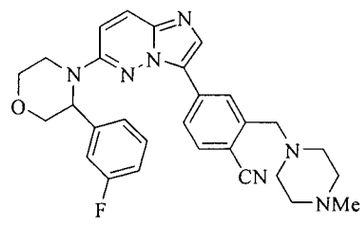
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		5.17 (m, 1H), 1.46 (dd, 1H), 4.00 (m, 3H), 3.76 (m, 1H), 3.66 (m, 1H); *m/z* 400 (M+1)
4		^{1}H RMN $CDCl_3$ δ (ppm) 8.72 (s, 1H), 8.49 (d, 1H), 8.30 (s, 1H), 8.08 (d, 1H), 7.84 (t, 1H), 7.39 (m, 1H), 7.26 (m, 2H), 7.03 (m, 2H), 6.91 (m, 1H), 5.08 (s, 1H), 4.22 (dd, 1H), 4.06 (m, 2H), 3.92 (m, 1H), 3.81 (m, 1H), 3.67 (m, 1H); *m/z* 376 (M+1)
5		*m/z* 401 (M+1)

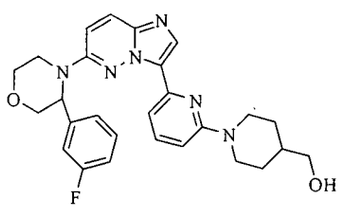
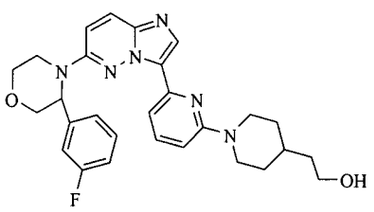
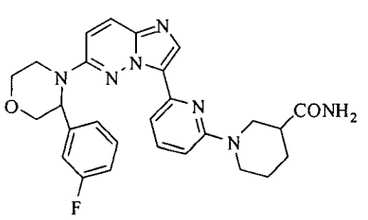
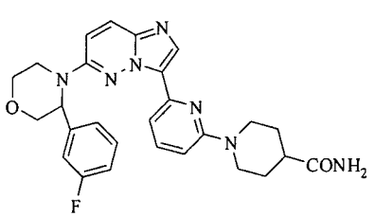
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
6		*m/z* 418 (M+1)
7		*m/z* 499 (M+1)
8		*m/z* 569 (M+1)
9		*m/z* 394 (M+1)

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
10		^{1}H RMN metanol-d4 δ (ppm) 8.43 (s, 1H), 8.12 (d, 1H), 7.69 (m, 3H), 7.34 (m, 1H), 7.25 (m, 2H), 7.00 (m, 1H), 6.88 (dd, 1H), 5.39 (m, 1H), 4.33 (dd, 1H), 4.15 (m, 3H), 3.82 (m, 6H), 3.58 (m, 4H); *m/z* 461 (M+1)
11		^{1}H RMN metanol-d4 δ (ppm) 8.50 (s, 1H), 8.14 (d, 1H), 7.77 (m, 3H), 7.36 (m, 1H), 7.36 (m, 2H), 7.01 (m, 2H), 5.40 (m, 1H), 4.34 (dd, 1H), 4.14 (m, 3H), 3.91 (m, 6H), 3.77 (m, 1H), 3.34 (m, 5H); *m/z* 460 (M+1)
12		*m/z* 484 (M+1)

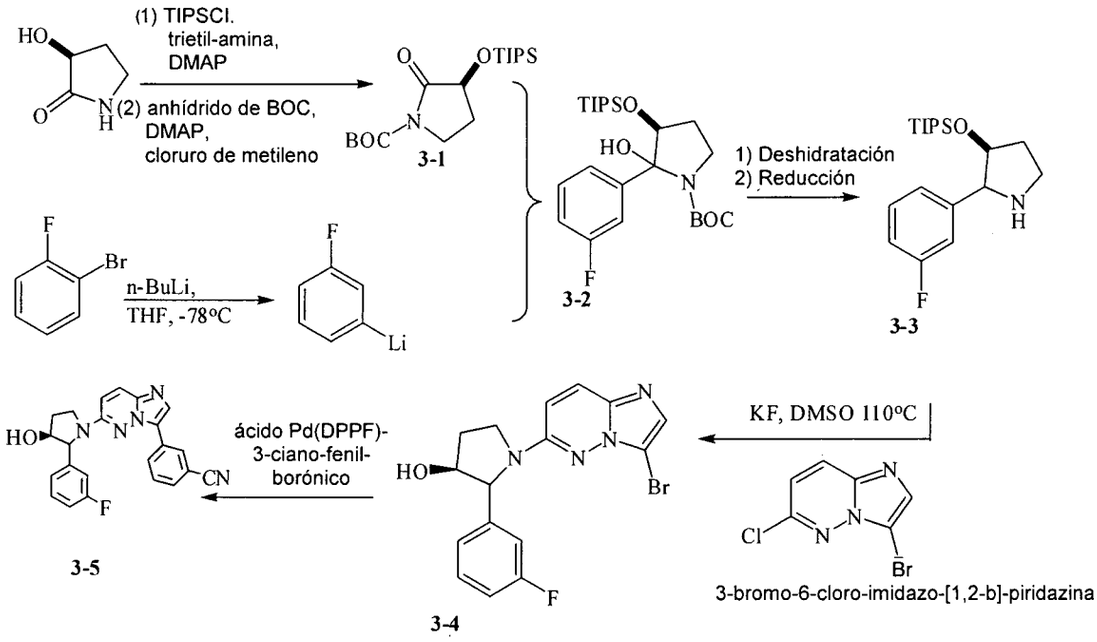
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
13		^{1}H RMN metanol-d4 δ (ppm) 8.31 (d, 1H), 8.22 (s, 1H), 8.12 (m, 2H), 7.72 (d, 1H), 7.34 (m, 2H), 7.23 (d, 1H), 7.16 (m, 1H), 6.97 (m, 1H), 5.29 (m, 1H), 4.27 (dd, 1H), 4.05 (m, 3H), 3.86 (m, 3H), 3.72 (m, 3H), 3.45 (m, 4H), 3.03 (s, 3H); *m/z* 498 (M+1)
14		*m/z* 526 (M+1)
15		*m/z* 475 (M+1)

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
16		*m/z* 560 (M+1)
17		^{1}H RMN DMSO-d6 δ (ppm) 8.12 (m, 1H), 7.95 (m,1H), 7.59 (d, 1H), 7.51 (t, 1H), 7.20 (m, 4H), 6.97 (td, 1H), 6.71 (d, 1H), 5.23 (m, 1H), 4.16 (m, 3H), 3.97 (m, 3H), 3.71 (td, 1H), 3.56 (m, 3H), 2.33 (m, 2H), 1.12 (s, 3H), 1.10 (s, 3H); *m/z* 489 (M+1)
18		*m/z* 475 (M+1)

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
19		^{1}H RMN metanol-d4 δ (ppm) 8.18 (s, 1H), 8.12 (d, 1H), 7.73 (m, 2H), 7.56 (dd, 1H), 7.34 (d, 1H), 7.28 (m,1H), 7.20 (m, 2H), 6.96 (m, 1H), 5.29 (m, 1H), 4.51 (m, 1H), 4.36 (m, 3H), 4.18 (q, 2H), 4.09 (m, 3H), 3.87 (td, 1H), 3.74 (m, 1H), 3.00 (m, 2H), 2.41 (m, 2H), 1.85 (m, 2H), 1.31 (t, 3H); *m/z* 586 (M+1)
20		MS *m/z* 475 (M+1)
21		MS *m/z* 512 (M+1)

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
22		MS *m/z* 489 (M+1)
23		MS *m/z* 503 (M+1)
24		MS *m/z* 502 (M+1)
25		MS *m/z* 502 (M+1)

Esquema 3



Ejemplo 3

3-(6-((3S)-2-(3-fluoro-fenil)-3-hidroxi-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo

El 3-(6-((3S)-2-(3-fluoro-fenil)-3-hidroxi-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo (3-5) se sintetizó en cinco pasos como se muestra en el esquema 3.

En el paso 3-1, se agregaron por goteo trietil-amina (20 mililitros, 139 milimoles), p-N,N-dimetil-amino-piridina (150 miligramos, 1 milimol), y luego cloruro de tri-isopropil-sililo (22.6 gramos, 118 milimoles) durante 4 minutos, a una solución de *S*-3-hidroxi-2-pirrolidinona (4.00 gramos, 39.6 milimoles) en 40 mililitros de cloruro de metileno. La mezcla de reacción se agitó durante 3 días y entonces se apagó con 200 mililitros de salmuera. La solución

se extrajo con acetato de etilo (300 mililitros, 3 veces), y los extractos orgánicos se concentraron utilizando un evaporador giratorio. Entonces el producto se utilizó directamente sin más purificación. El residuo se disolvió en 100 mililitros de cloruro de metileno y 50 mililitros de trietil-amina (co-solvente), y se trató con p-N,N-dimetil-amino-piridina (100 miligramos, 0.8 milimoles), seguida por anhídrido de Boc (22.9 gramos, 104 milimoles). La mezcla de reacción se agitó vigorosamente durante 6 horas, se apagó con 100 mililitros de salmuera, y se extrajo con 200 mililitros de acetato de etilo. Los extractos orgánicos se concentraron y entonces se purificaron utilizando cromatografía por evaporación instantánea (sistema de solvente isocrático desde el 10 por ciento de acetato de etilo hasta hexanos), proporcionando el 2-oxo-3-(tri-isopropil-sililoxi)-pirrolidin-1-carboxilato de (S)-terbutilo (3-1) como un aceite. ^{1}H RMN (400 MHz, D_3 acetonitrilo) δ ppm 4.50 (t, *J* = 8.0 Hz, 1H), 3.70 (t, *J* = 8.2, 1H), 3.44-3.39 (m, 1H), 2.40-2.30 (m, 1H), 1.96-1.80 (m, 1H), 1.52 (s, 9H), 1.21-1.05 (m, 21H). LCMS observada *m/z* 737.5 ion mayor (calculado para 2M+Na, 737.5).

En el paso 3-2, una solución de 3-fluoro-1-bromo-benceno (4.0 gramos, 22.9 milimoles) en tetrahidrofurano (10 mililitros), se enfrió a -60°C. A esta solución se le agregó una solución de n-BuLi en hexanos (hexanos 1.6 M, 14.3 mililitros, 22.9 milimoles), durante 12 minutos, permitiendo tener una rampa de temperatura gradual (2°C/minuto) hasta que se obtuvo una temperatura interna neta de -40°C y se agregó todo el n-BuLi. Entonces la mezcla de reacción se

dejó calentar durante un periodo de 30 minutos hasta que se alcanzó una temperatura interna de -22°C, entonces la solución resultante (en color oscuro) se enfrió a -45°C, y entonces se le agregó una solución de 2-oxo-3-(tri-isopropil-sililoxi)-pirrolidin-1-carboxilato de (S)-terbutilo (2.0 gramos, 5.6 milimoles) en tetrahidrofurano (10 mililitros), durante 6 minutos (no se permitió que la temperatura interna excediera de -40°C durante este evento de adición). La mezcla entonces se dejó calentar a -20°C durante un periodo de 35 minutos y entonces la temperatura se mantuvo a -20°C durante 2 horas. La mezcla de reacción entonces se apagó con una solución fría acuosa saturada de cloruro de amonio (150 mililitros), se calentó a temperatura ambiente, y se extrajo con acetato de etilo (150 mililitros, 3 veces). Los extractos orgánicos se combinaron, se concentraron utilizando un evaporador giratorio, y se purificaron usando cromatografía por evaporación instantánea (gradiente de acetato de etilo al 5 por ciento en hexanos hasta acetato de etilo al 10 por ciento en hexanos durante 30 minutos), proporcionando el racemato de 2-(3-fluoro-fenil)-2-hidroxi-3-(tri-isopropil-sililoxi)-pirrolidin-1-carboxilato de (3S)-terbutilo (3-2) como un aceite. ^{1}H RMN (400 MHz, D_6 acetona) δ ppm 7.92-7.23 (m, 4H), 5.80 (br s, 1H), 5.10 (app t, *J* = 8.2, 1H), 3.20-2.95 (m, 2H), 2.05-1.95 (m, 2H), 1.35 (s, 9H), 1.21-0.99 (m, 21H). LCMS observada *m/z* 737.5 ion mayor.

En el paso 3-3, se agregó una solución de HCl 4N-dioxano (3 mililitros), a una solución de 2-(3-fluoro-fenil)-2-hidroxi-3-(tri-

isopropil-sililoxi)-pirrolidin-1-carboxilato de (3S)-terbutilo (1.1 gramos, 2.4 milimoles) en metanol (30 mililitros), y se agitó durante 6 horas a temperatura ambiente. La mezcla de reacción se apagó con bicarbonato de sodio (4 gramos, 48 milimoles), y la pasta acuosa resultante se trató con borohidruro de sodio sólido (3 gramos, 79 milimoles), y se agitó durante 4 horas. Se agregaron 200 mililitros de salmuera a la mezcla de reacción, y la solución se extrajo con acetato de etilo (200 mililitros, 2 veces), y se purificó mediante cromatografía en fase inversa C-18 con un gradiente de agua/acetonitrilo de 90:10 a 10:90), para proporcionar la (3S)-2-(3-fluoro-fenil)-3-(tri-isopropil-sililoxi)-pirrolidina (3-3) como un aceite rojo oscuro (mezcla de diaestereómeros). ^{1}H RMN (400 MHz, D_3 acetonitrilo) δ ppm 7.62-7.57 (m, 1H), 7.56-7.43 (m, 3H), 4.90-4.80 (m, 1H), 3.85-3.53 (m, 2H), 2.60-2.50 (m, 2H), 1.96-1.80 (m, 1H), 1.52 (s, 9H), 1.21-1.05 (m, 21H). LCMS observada m/z 338.2 ion mayor.

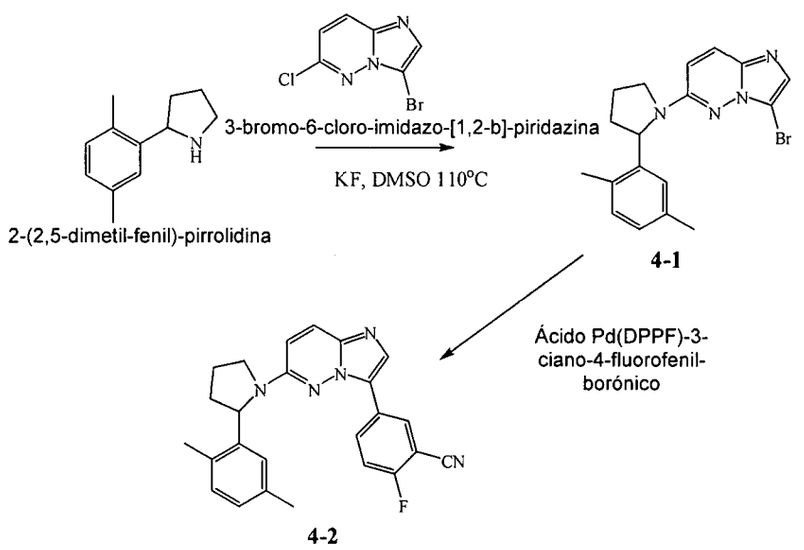
En el paso 3-4, se agregaron KF (100 miligramos, 1.72 milimoles), y 3-bromo-6-cloro-imidazo-[1,2-b]-piridazina (12-1) (700 miligramos, 3.0 milimoles) a una solución de (3S)-2-(3-fluoro-fenil)-3-(tri-isopropil-sililoxi)-pirrolidina (4-3) (700 gramos, 2.0 milimoles) en 3 mililitros de DMSO. La pasta acuosa resultante se calentó a 110°C durante 6 horas y entonces se enfrió, se diluyó con 8 mililitros de metanol, y se purificó utilizando cromatografía en fase inversa C-18 (gradiente de agua/acetonitrilo de 90:10 a 10:90), para proporcionar el (3S)-1-(3-bromo-imidazo-[1,2-b]-piridazin-6-il)-2-(3-fluoro-fenil)-

pirrolidin-3-ol (3-4) como un sólido (mezcla de diaestereómeros). ^{1}H RMN (400 MHz, D_6 acetona) δ ppm 8.20 (app t, *J*= 6.5 Hz, 1H), 7.85-6.70 (m, 6H), 5.05 (app d, *J*= 5.5 Hz, 1H), 4.68 (app q, *J*= 7.5 Hz, 1H), 4.30 (br s, 1H), 4.01-3.92 (m, 1H), 3.82-3.70 (m, 1H), 2.35-1.87 (m, 2H). LCMS observada m/z 377.1, 379.1 ion mayor.

En el paso 3-5, en un envase de microondas, se agregaron carbonato de sodio (105 miligramos, 1.0 milimoles), ácido 3-ciano-fenil-borónico (200 miligramos, 1.36 milimoles), y aducto de catalizador de Pd(DPPF)-dicloruro / (1,1'bis-(difenil-fosfino-ferroceno)-dicloro-paladio(II) con dicloro-metano) (100 miligramos, 0.12 milimoles) a una solución de (3S)-1-(3-bromo-imidazo-[1,2-b]-piridazin-6-il)-2-(3-fluoro-fenil)-pirrolidin-3-ol (1.40 gramos, 0.36 milimoles), y 4 mililitros de 1,4-dioxano/agua (3:1). Entonces, esta solución se sometió a las siguientes condiciones de microondas utilizando un instrumento de microondas de laboratorio (condiciones: 150°C, umbral máximo de 200 W, presión máxima de 20 atmósferas, tiempo de reacción de 20 minutos). La mezcla de reacción se purificó directamente mediante HPLC en fase inversa C-18 (gradiente de agua/acetonitrilo de 90:10 a 10:90), para proporcionar el 3-(6-((3S)-2-(3-fluoro-fenil)-3-hidroxi-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo (3-5) como una mezcla de diaestereómeros. ^{1}H RMN (400 MHz, D_6 acetona) δ ppm 8.85 (br s, 1H), 8.40-8.03 (m, 3 H),7.90-7.22 (m, 5 H), 7.10 (app d, *J*= 5.5 Hz, 1H), 6.98 (app t, *J*= 4.5 Hz, 1H), 5.25 (app d, *J*= 4.5 Hz, 1H), 4.80 (app q, *J*= 7.5 Hz, 1H), 4.30 (br s, 1H), 3.82-3.75 (m, 1H), 3.3-3.55 (m, 1H), 2.42-2.34 (m,

1H), 2.25-2.12 (m, 1H). LCMS observada m/z 400.2.

Esquema 4



Ejemplo 4

5-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-1-(piperidin-4-il)-1H-benzo-[d]-imidazol-2(3H)-ona

El 5-(6-(2-(2,5-dimetil-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-fluoro-benzonitrilo (5-2) se sintetizó en dos pasos como se muestra en el esquema 4.

En el paso 4-1, se agregaron fluoruro de potasio (58 miligramos, 1.0 milimoles) y (3-bromo-6-cloro-imidazo-[1,2-b]-piridazina (12-1) (100 miligramos, 0.43 milimoles) a una solución de 2-(2,5-dimetil-fenil)-pirrolidina (100 miligramos, 0.57 milimoles) en 3 mililitros de DMSO. La mezcla de reacción se calentó a 130°C, y se agitó durante 6 horas a 130°C. La mezcla de reacción se enfrió a temperatura ambiente, y se purificó utilizando cromatografía en fase normal por evaporación instantánea con acetato de etilo y hexanos

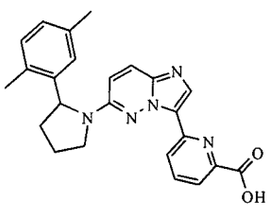
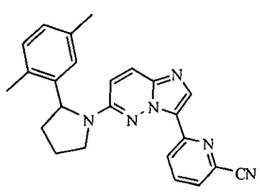
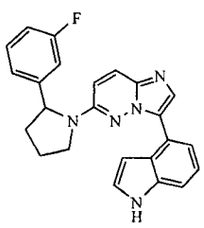
(1:1) como una fase móvil para proporcionar la 3-bromo-6-(2-(2,5-dimetil-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina (4-1) como su mezcla racémica. ^{1}H RMN (400 MHz, D_3 acetonitrilo) δ ppm 7.50 (app d, *J*= 9.5 Hz, 1H), 7.40 (br s, 1H), 7.08 (d, *J*= 6.5 Hz, 1H), 6.92 (d, *J*= 6.6 Hz, 1H), 6.82 (br s, 1H), 6.58 (br d, *J*= 9.5 Hz, 1H), 5.28 (br d, *J*= 5.0 Hz, 1H), 4.08-3.95 (m, 1H), 3.62 (app q, *J*= 6.4 Hz, 1H), 3.30 (s,1H), 2.51-2.42 (m, 1H), 2.24 (br s, 6H), 2.17-2.04 (m, 2H) . LCMS observada m/z 371.1, 373.1 ion mayor.

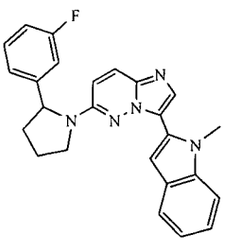
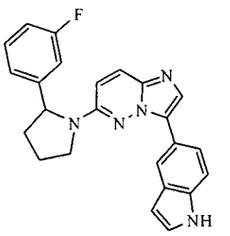
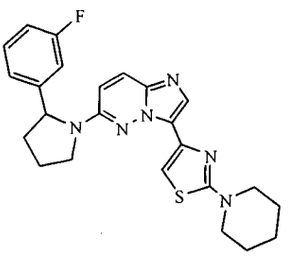
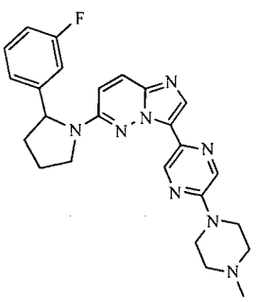
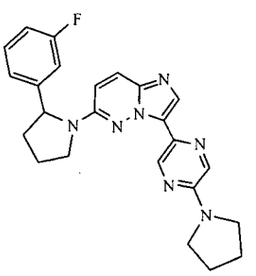
En el paso 4-2, se agregaron carbonato de sodio (30 miligramos, 0.30 milimoles), ácido 3-ciano-4-fluoro-fenil-borónico (30 miligramos, 0.24 milimoles), y aducto de catalizador de Pd(DPPF)-dicloruro/(1,1'bis-(difenil-fosfino-ferroceno)-dicloro-paladio(II) con dicloro-metano) (10 miligramos, 0.012 milimoles), en un envase de microondas que contenía una solución de 3-bromo-6-(2-(2,5-dimetil-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina (50 miligramos, 0.13 milimoles), y 2.5 mililitros de 1,4-dioxano/agua (3:1). La mezcla de reacción se sometió a las siguientes condiciones de microondas utilizando un instrumento de microondas de laboratorio (condiciones: 150°C, umbral máximo de 200 W, presión máxima de 20 atmósferas, tiempo de reacción de 20 minutos). La solución resultante se purificó utilizando LC/MS de preparación (cromatografía en fase inversa C-18), para proporcionar el 5-(6-(2-(2,5-dimetil-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-fluoro-benzonitrilo (4-2). ^{1}H RMN (400 MHz, D_3 acetonitrilo) δ ppm 8.50-8.10 (m, 2H), 7.80 (br s, 1H), 7.50 (app d, *J*= 8.5 Hz, 1H), 7.20 (app t, *J*= 6.5 Hz, 1H), 7.06 (d, *J*=

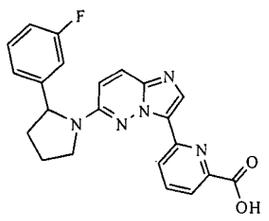
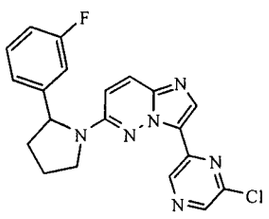
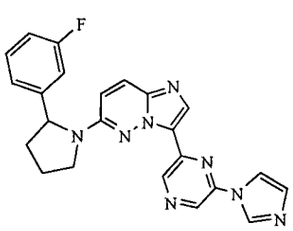
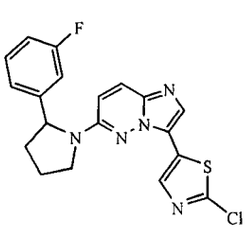
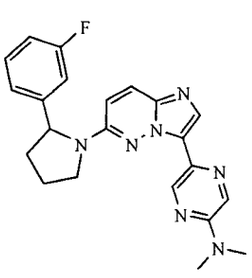
6.5 Hz, 1H), 6.93 (d, *J*= 6.6 Hz, 1H), 6.81 (br s, 1H), 6.60 (br s, 1H), 5.22 (app dd, *J*= 6.2, 2.1 Hz, 1H), 4.05-4.00 (m, 1H), 3.76 (app q, *J*= 6.4 Hz, 1H), 3.36 (app d, *J*= 2.2 Hz, 1H), 2.58-2.43 (m, 1H), 2.24 (br s, 6H), 2.19-2.08 (m, 2H) . LCMS observada m/z 412.2.

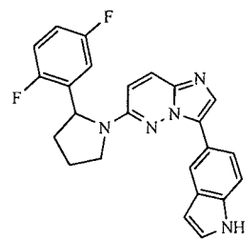
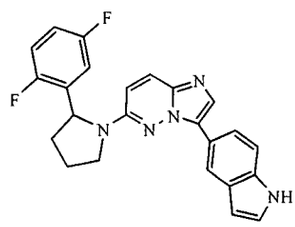
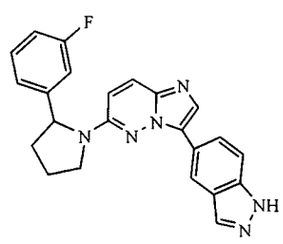
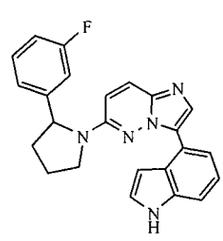
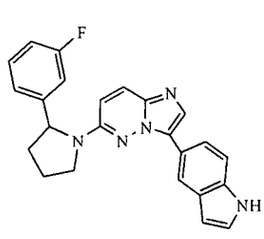
Mediante la repetición de los procedimientos descritos en los ejemplos anteriores, utilizando los materiales de partida apropiados, se obtuvieron los siguientes compuestos de la fórmula I, como se definen en la Tabla 3.

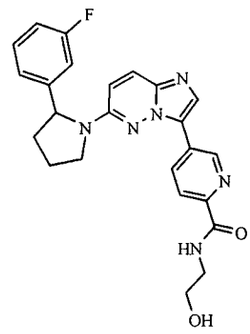
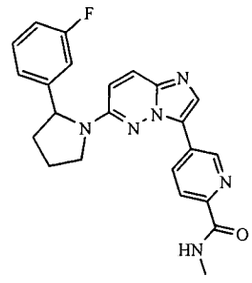
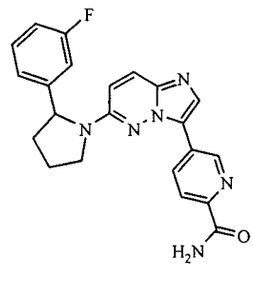
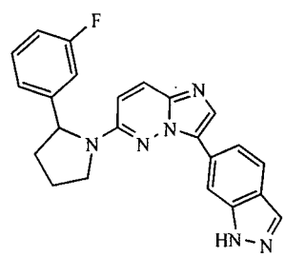
Tabla 3

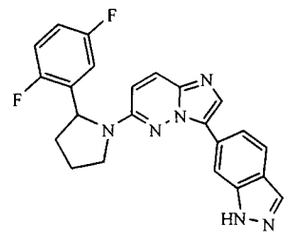
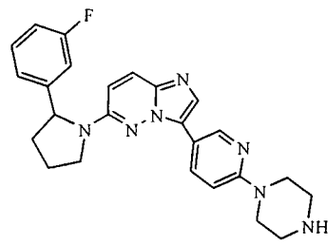
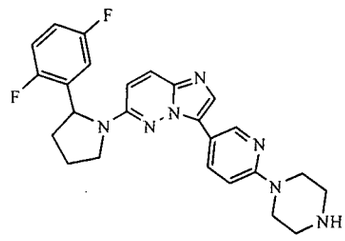
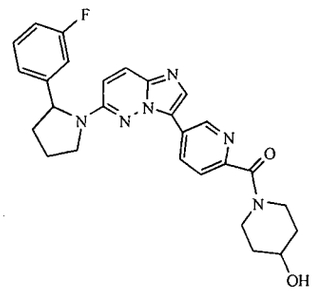
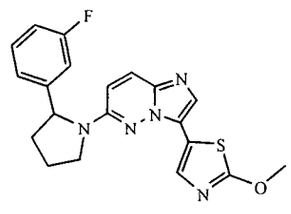
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
1		*m/z* 414.2 (M+1)
2		*m/z* 395.2 (M+1)
3		*m/z* 398.2 (M+1)

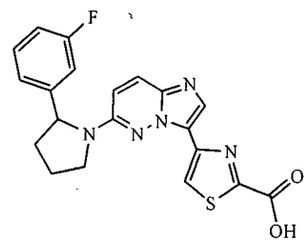
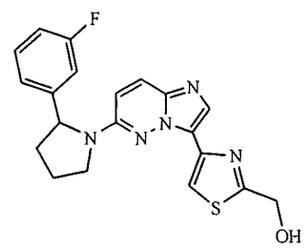
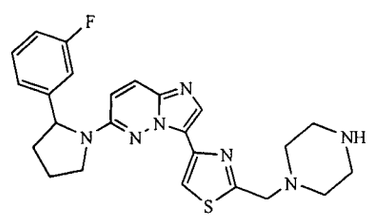
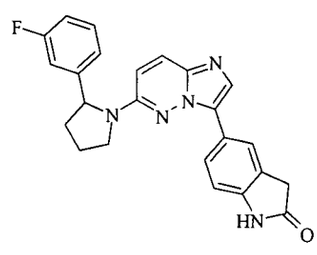
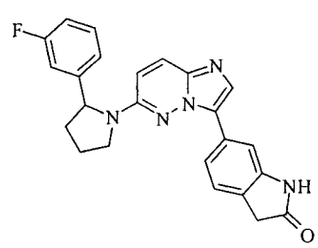
4		*m/z* 412.2 (M+1)
5		*m/z* 398.2 (M+1)
6		*m/z* 449.2 (M+1)
7		*m/z* 459.2 (M+1)
8		*m/z* 430.2 (M+1)

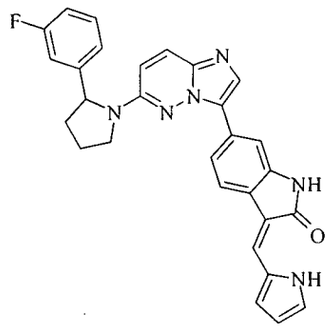
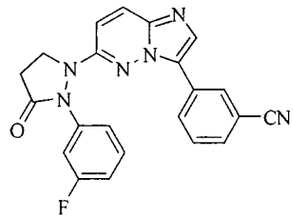
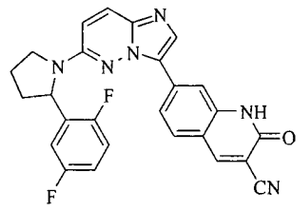
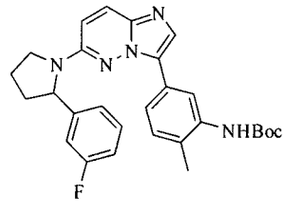
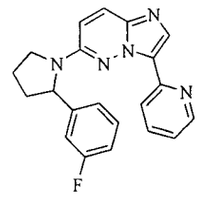
9		*m/z* 404.2 (M+1)
10		*m/z* 395.2 (M+1)
11		*m/z* 427.2 (M+1)
12		*m/z* 400.6 (M+1)
13		*m/z* 404.2 (M+1)

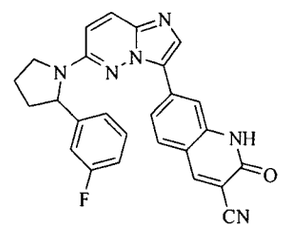
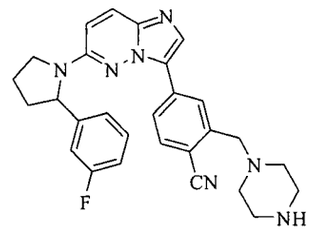
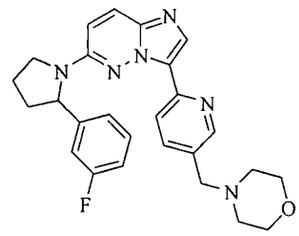
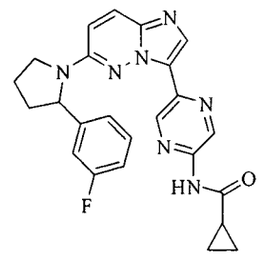
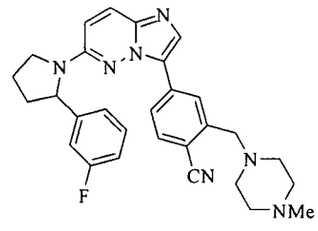
14		*m/z* 416.2 (M+1)
15		*m/z* 416.2 (M+1)
16		*m/z* 399.2 (M+1)
17		*m/z* 398.2 (M+1)
18		*m/z* 398.2 (M+1)

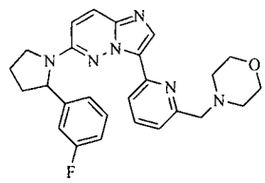
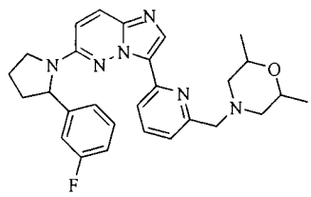
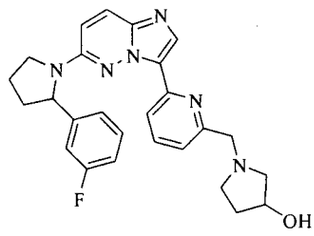
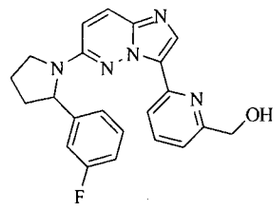
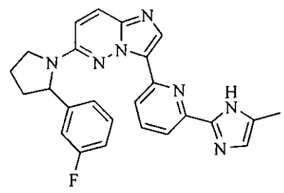
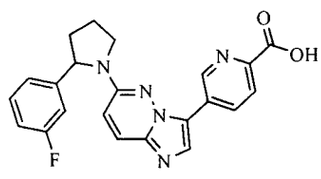
19		*m/z* 447.2 (M+1)
20		*m/z* 417.2 (M+1)
21		*m/z* 404.2 (M+1)
22		*m/z* 399.2 (M+1)

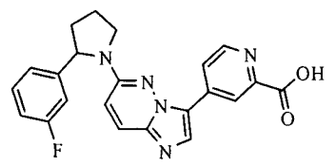
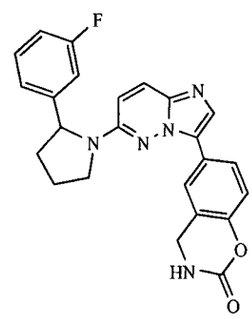
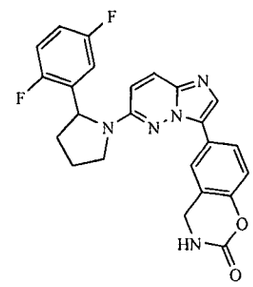
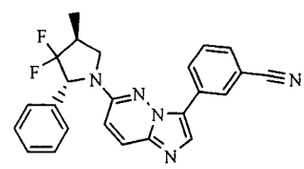
23		*m/z* 417.2 (M+1)
24		*m/z* 444.5 (M+1)
25		*m/z* 462.2 (M+1)
26		*m/z* 487.3 (M+1)
27		*m/z* 396.2 (M+1)

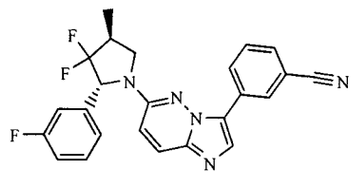
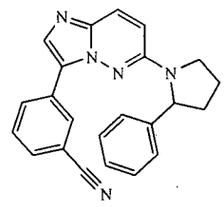
28		*m/z* 410.2 (M+1)
29		*m/z* 396.2 (M+1)
30		*m/z* 464.2 (M+1)
31		*m/z* 414 (M+1)
32		^{1}H RMN DMSO-d6 δ (ppm) 10.64 (s, 1H), 8.31 (m, 1H), 8.05 (m, 1H), 7.64 (m, 1H), 7.35 (m, 2H), 7.13 (m,5H), 5.23 (m 1H), 4.01 (m, 2H), 3.69 (m, 1H), 3.56 (s, 2H),

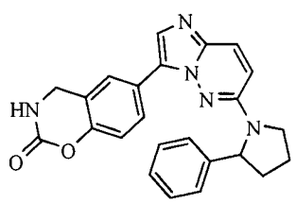
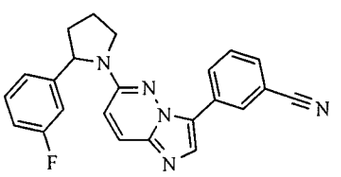
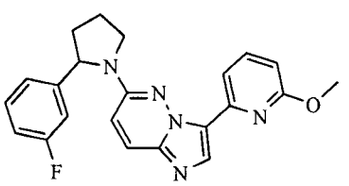
		2.05 (m, 2H), 1.91 (m, 1H); *m/z* 414 (M+1)
33		*m/z* 491 (M+1)
34		MS *m/z* 399 (M+1)
35		MS *m/z* 469 (M+1)
36		MS *m/z* 488 (M+1)
37		MS *m/z* 360 (M+1)

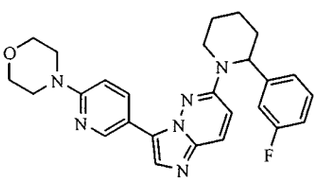
38		MS *m/z* 451 (M+1)
39		MS *m/z* 482 (M+1)
40		MS *m/z* 459 (M+1)
41		MS *m/z* 444 (M+1)
42		MS *m/z* 496 (M+1)

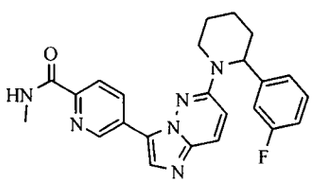
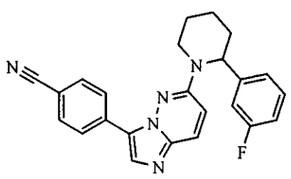
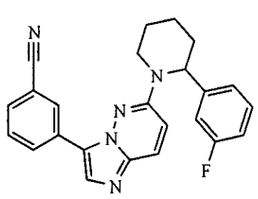
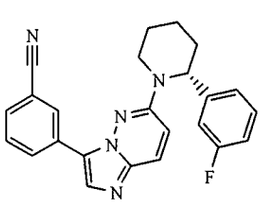
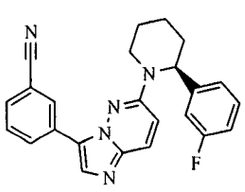
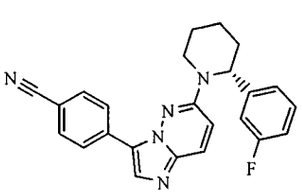
43		MS *m/z* 459 (M+1)
44		MS *m/z* 487 (M+1)
45		MS *m/z* 459 (M+1)
46		MS *m/z* 389 (M+1)
47		MS m/z 440 (M+1)
48		*m/z* 404.2 (M+1)

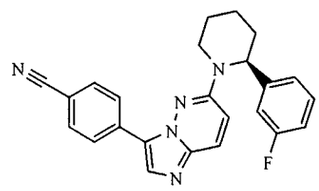
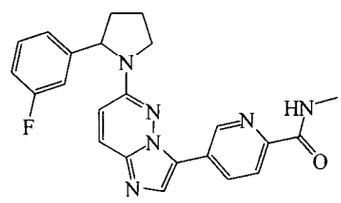
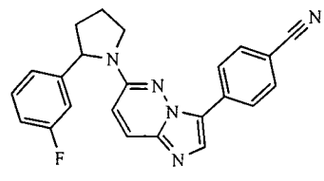
49		*m/z* 404.2 (M+1)
50		^{1}H RMN (DMSO-d6): δ 8.02 (s, 1 H), 7.90 (s, 1 H), 7.88 (s, 1 H), 7.86 (s, 1 H), 7.37-7.40 (m, 1 H), 7.14 (d, 2 H), 7.05 (t, 1 H), 6.95 (d, 1 H), 6.81 (d, 1 H), 5.18 (d, 1 H), 4.40-4.45 (m, 1 H), 4.30-4.40 (m, 1 H), 3.95-3.99 (m, 1H), 3.62-3.66 (m, 1H),; 2.43-2.49 (m, 1H), 1.95-2.05 (m, 2H), 1.85-1.90 (m, 1H) *m/z* 430.4 (M+1)
51		*m/z* 448.4 (M+1)
52		^{1}H RMN (DMSO-d6): d 8.49 (s, 1 H), 8.18-8.24 (m, 1 H), 8.16 (s, 1 H), 8.00 (d, 1 H),

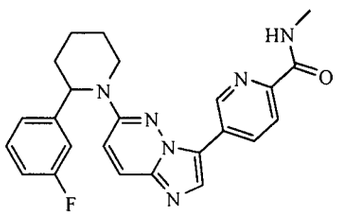
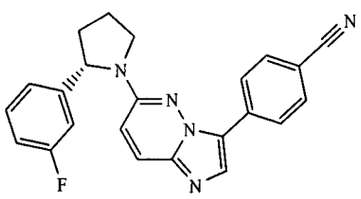
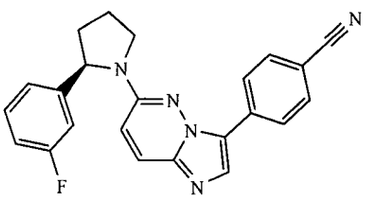
		7.73 (d, 1 H), 7.56 (t, 1 H), 7.49 (d, 2 H), 7.40 (t, 2 H), 7.32 (t, 1 H), 6.88-6.96 (m, 1 H), 5.43 (d, 1 H), 4.37 (t, 1 H), 3.40 (t, 1H), 2.76-2.94 (m, 1H), 1.17 (d, 3H) *m/z* 416.4 (M+1)
53		^{1}H RMN (DMSO-d6): 8.55 (s, 1 H), 8.18-8.25 (m, 1 H), 8.16 (s, 1 H), 8.00 (d, 1 H), 7.74 (d, 1 H), 7.55 (t, 1 H), 7.42-7.49 (m, 1 H), 7.33-7.39 (m, 2 H), 7.11-7.19 (m, 1 H), 6.88-6.98 (m, 1 H), 5.47 (d, 1 H), 4.38 (t, 1 H), 3.86 (t, 1H), 2.78-2.94 (m, 1H), 1.17 (d, 3H) *m/z* 434.4 (M+1)
54		H RMN (DMSO-d6) d 855 (s, 1 H), 8.20-8.32 (bs, 1 H), 8.12 (s, 1H), 7.89 (d, 1 H), 7.71 (d, 1 H), 7.54 (t, 1 H), 7.26-7.36 (m, 4 H), 7.18-

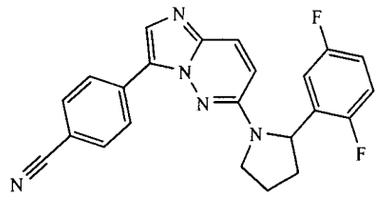
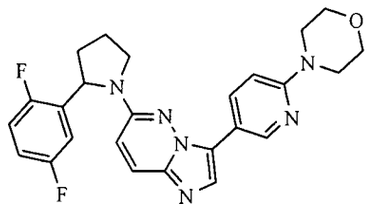
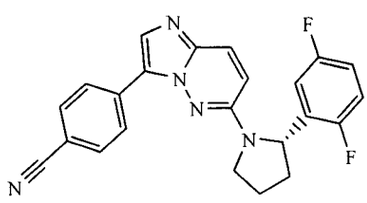
		7.24 (m, 1 H), 6.76-6.91 (bs, 1 H), 5.15-5.21 (m, 1 H), 3.94-4.02 (m, 1 H), 3.66-3.72 (m, 1 H), 2.45-2.50 (m, 1 H), 2.01-2.08 (m, 2 H), 1.82-1.90 (m, 1 H) *m/z* 366.4 (M+1)
55		*m/z* 412.5 (M+1)
56		*m/z* 384.4 (M+1)
57		^{1}H RMN (DMSO-d6) 8.14 (s, 1 H), 7.91 (s, 1 H), 7.58-7.64 (m, 2 H), 7.53-7.57 (m, 1 H), 7.35-7.41 (m, 1 H), 7.15-7.17 (m, 2 H), 7.01-7.05 (m, 1 H), 6.68 (d, 1 H), 5.16-5.19 (q, 1 H), 3.98-4.02 (m, 1 H), 3.91 (s, 3 H), 3.65-3.71 (m, 1 H), 2.44-2.49 (m,

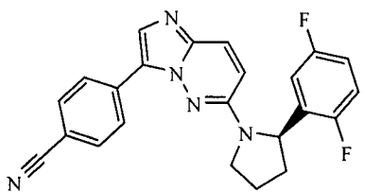
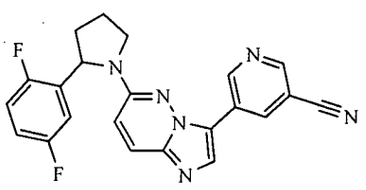
		1 H), 2.01-2.07 (m, 2 H), 1.85-1.90 (m, 1 H) *m/z* 390.4 (M+1)
58		H RMN (DMSO-d6, 400MHz) 8.725 (d, J= 0.005, 1H) 8.374 (s, 1H) 8.195 (d, J = 0.025, 1H) 8.074 (dd, J = 0.023, 0.006, 1H) 7.705 (d, J = 0.026, 1H) 7.406 (q, J = 0.02, 1H) 7.149 (s, 1H) 7.129 (s, 1H) 7.082 (dt, J = 0.015, 0.005, 1H) 6.973 (d, J = 0.023, 1H) 5.561 (t, J = 0.01, 1H) 4.270 (d, J = 0.033, 1H) 3.725 (t, J = 0.011, 4H) 3.561 (t, J = 0.013, 4H) 3.317 (dt, J = 0.035, 0.01, 1H) 2.265 (m, 1H) 20.39 (m, 1H) 1.782 (m, 1H) 1.649 (m, 2H) 1.455 (m, 1H) *m/z* 459.2 (M+1)

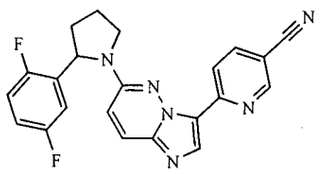
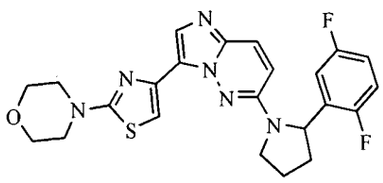
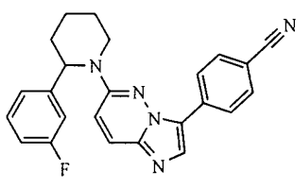
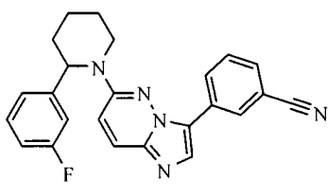
59		*m/z* 431.2 (M+1)
60		*m/z* 398.2 (M+1)
61		*m/z* 398.2 (M+1)
62		*m/z* 398.2 (M+1)
63		*m/z* 398.2 (M+1)
64		*m/z* 398.2 (M+1)

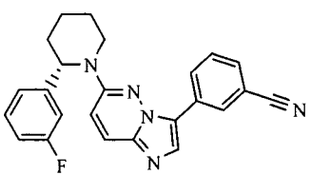
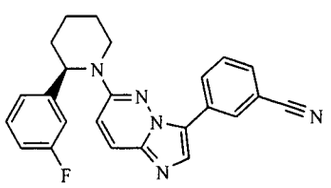
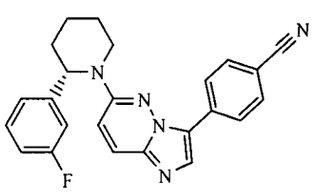
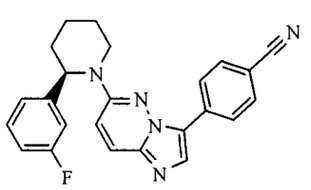
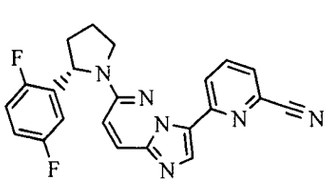
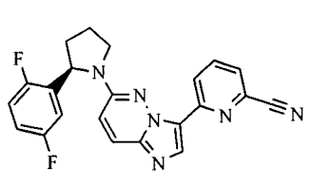
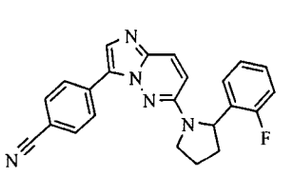
65		*m/z* 398.2 (M+1)
66		H RMN (DMSO-d6, 400MHz) 9.198 (br.s, 1H) 8.790 (ds, J = 0.011, 1H) 8.504 (s, 1H) 8.102 (d, J = 0.025, 1H) 8.008 (br.s, 1H) 7.377 (q, J = 0.019, 1H) 7.166 (d, J = 0.019) 7.166 (m, 3H) 7.083 (dt, J = 0.019, 0.004, 1H) 5.192 (d, J = 0.017, 1H)4.011 (m, 1H) 3.695 (q, J = 0.025, 1H) 2.868 (d, J = 0.012, 3H) 2.451 (m, 1H) 2.056 (m, 2H), 1.898 (m, 1H) *m/z* 417.5 (M+1)
67		*m/z* 384.4 (M+1)

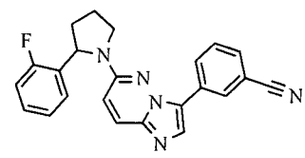
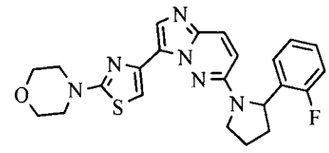
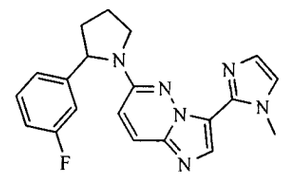
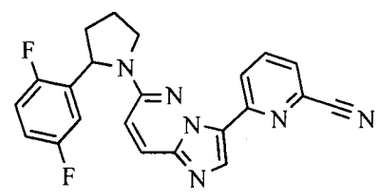
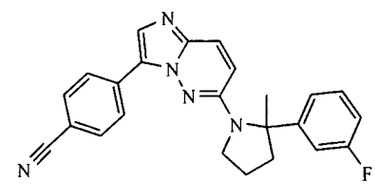
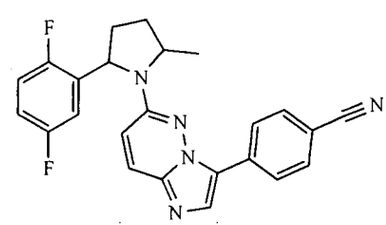
68		*m/z* 431.5 (M+1)
69		H RMN (DMSO-d6, 400MHz) 8.205 (br.s, 2H) 7.994 (d, J = 0.025, 1H) 7.815 (d, J = 0.019, 2H) 7.486 (q, J = 0.021, 1H) 7.222 (m, 2H) 7.108 (dt, J = 0.023, 0.006, 1H) 6.959 (br.s, 1H) 5.209 (dd, J = 0.021, 0.007, 1H) 4.048 (p, J = 0.014, 1H) 3.719 (q, J = 0.02, 1H) 2.513 (m, 1H), 2.092 (m, 2H) 1.919 (m, 1H) *m/z* 384.4 (M+1)
70		H RMN (DMSO-d6, 400MHz) 8.084 (br.s, 2H) 7.875 (d, J = 0.024, 1H) 7.697 (d, J = 0.02, 2H) 7.364 (q, J = 0.02, 1H) 7.100 (m, 2H) 6.985 (dt, J = 0.023, 0.006, 2H) 6.841 (br.s, 1H)5.091 (dd, J = 0.02, 0.006, 1H) 3.928 (p, J

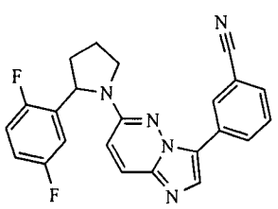
		= 0.014 1H) 3.600 (q, J = 0.021, 1H) 2.370 (m, 1H) 1.971 (m, 2H) 1.797 (m, 1H) *m/z* 384.4 (M+1)
71		*m/z* 402.4 (M+1)
72		H RMN (DMSO-d6, 400MHz) 8.572 (br.s, 1H) 7.739 (m, 3H) 7.306 (m, 1H) 7.056 (m, 1H)7.056 (m, 1H) 6.954 (m, 1H) 6.739 (s, 1H) 6.638 (m, 1H) 5.203 (d, J = 0.016, 1H) 3.916 (m, 1H) 3.837 (m, 1H) 3.667 (m, 4H) 3.540 (m, 1H) 3.425 (m, 4H) 2.391 (m, 1H) 2.009 (m, 2H) 1.830 (m, 1H) *m/z* 463.5 (M+1)
73		H RMN (DMSO-d6, 400MHz) 8.094 (s, 1H) 7.998 (br.s, 2H) 7.917 (d, J = 0.024, 1H) 7.660 (d, J = 0.021 2H)

		7.423 (dq, J = 0.024, 0.011, 1H)7.061 (m, 1H) 6.992 (m, 1H) 6.925 (br.s, 1H) 5.248 (d, J = 0.019, 1H) 3.962 (m, 1H) 3.561 (q, J = 0.018, 1H) 2.382 (m, 1H) 1.998 (m, 2H) 1.830 (m, 1H) *m/z* 402.4 (M+1)
74		H RMN (DMSO-d6, 400MHz) 8.091 (s, (1H) 7.994 (br.s, 2H) 7.913 (d, J = 0.025, 1H) 7.655 (d, J = 0.02, 1H) 7.421 (dq, J = 0.021, 0.011, 1H) 7.059 (m, 1H) 6.989 (m, 1H) 6.925 (br.s, 1H) 5.242 (d, J = 0.019, 1H) 3.959 (m, 1H) 3.556 (q, J = 0.018, 1H) 2.390 (m, 1H) 1.997 (m, 2H) 1.819 (m, 1H) *m/z* 402.4 (M+1)
75		*m/z* 403.4 (M+1)

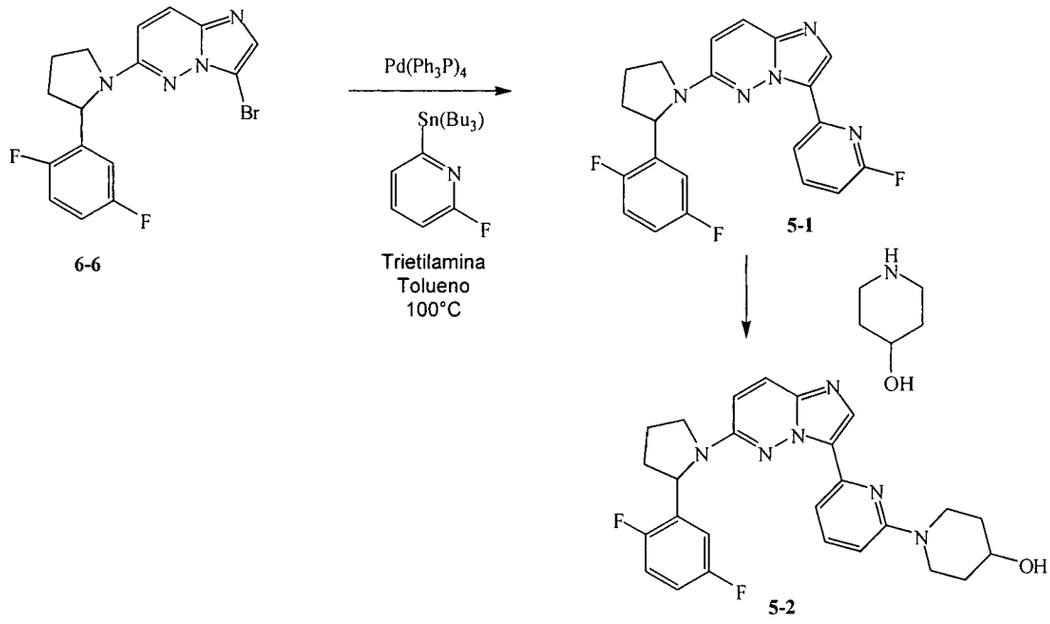
76		*m/z* 403.4 (M+1)
77		H RMN (DMSO-d6, 400MHz) 7.854 (d, J= 0.024, 1H) 7.710 (s, 1H) 7.248 (m, 1H) 7.072 (m, 1H) 6.979 (m, 1H) 6.801 (m, 1H), 6.694 (m, 1H) 5.274 (d, J = 0.019, 1H) 3.948 (dt, J = 0.025, 0.007, 1H) 3.658 (t, 0.011, 4H), 3.572 (q, J = 0.024, 1H) 3.359 (t, J = 0.012, 3H) 2.007 (m, 3H) 1.285 (s, 1H) 1.164 (s, 1H) *m/z* 469.5 (M+1)
78		*m/z* 398.4 (M+1)
79		*m/z* 398.4 (M+1)

80		*m/z* 398.4 (M+1)
81		*m/z* 398.4 (M+1)
82		*m/z* 398.4 (M+1)
83		*m/z* 398.4 (M+1)
84		*m/z* 403.4 (M+1)
85		*m/z* 403.4 (M+1)
86		*m/z* 384.4 (M+1)

87		*m/z* 384.4 (M+1)
88		*m/z* 451.5 (M+1)
89		*m/z* 363.4 (M+1)
90		*m/z* 403.4 (M+1)
91		*m/z* 398.4 (M+1)
92		8.166 (s, 1H) 8.019 (s, 1H) 7.998 (d, J = 0.01, 1H) 7.963 (s, 1H) 7.719 (d, J = 0.021, 2H) 7.514 (dq, J = 0.024, 0.011, 1H) 7.143 (m, 1H) 6.990 (m, 2H) 5.199 (t, J =

		0.02, 1H) 4.338 (d sexteto, J = 0.017, 0.006, 1H) 2.550 (m, 1H) 2.223 (m, 1H) 1.944 (m, 1H) 1.768 (m, 1H) 1.497 (d, J = 0.016, 3H) *m/z* 416.4 (M+1)
93		8.327 (br s, 1H) 8.123 (s, 2H) 7.938 (d, J = 0.025, 1H) 7.678 (d, J = 0.020, 1H) 7.423 (t, J = 0.020, 1H) 7.272 (m, 1H) 7.045 (m, 1H) 6.964 (m, 2H) 5.275 (d, J = 0.019, 1H) 3.967 (dt, J = 0.024, 0.006, 1H) 3.564 (q, J = 0.023, 2H) 1.998 (m, 3H) *m/z* 402.4 (M+1)

Esquema 5



Ejemplo 5

1-(6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol

El 1-(6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol (5-2) se sintetizó en dos pasos como se muestra en el esquema 5.

En el paso 5-1, se agregaron trietil-amina (0.045 mililitros, 0.29 milimoles), tetraquis-(trifenil-fosfina)-paladio(0) (12 miligramos, 0.01 milimoles), y 6-fluoro-2-(tributil-estanil)-piridina (80 miligramos, 0.201 milimoles) a una solución de 3-bromo-6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina (6-6) (53 miligramos, 0.13 milimoles) en 3 mililitros de tolueno. La mezcla de reacción se calentó a 100°C, y se agitó durante 6 horas a 100°C. La mezcla de reacción se enfrió entonces a temperatura ambiente, y se purificó

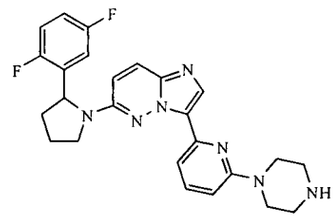
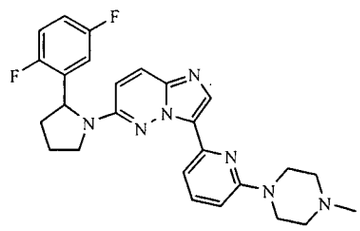
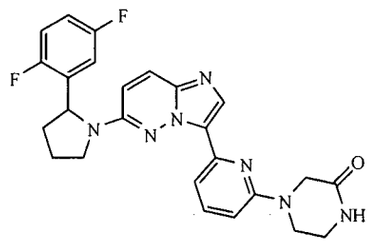
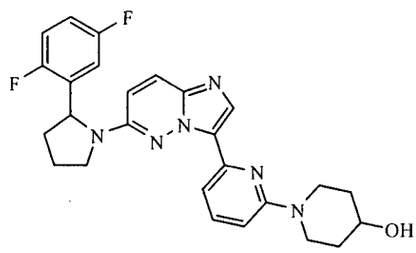
utilizando cromatografía por evaporación instantánea (acetato de etilo y hexanos (1:1)) dando la 6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(6-fluoro-piridin-2-il)-imidazo-[1,2-b]-piridazina (5-1). ^{1}H RMN (400 MHz, D_3 acetonitrilo) δ ppm 8.35-8.17 (m, 2H), 8.02-7.83 (m, 1H), 7.48-7.22 (m, 3H), 7.15-6.92 (m, 3H), 5.42 (br d, *J*= 5.8 Hz, 1H), 4.12-3.99 (m, 1H), 3.81-3.72 (m, 1H), 2.70-2.56 (m, 1H), 2.30-2.06 (m, 3H) . LCMS observada m/z 396.1

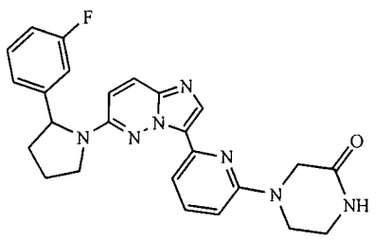
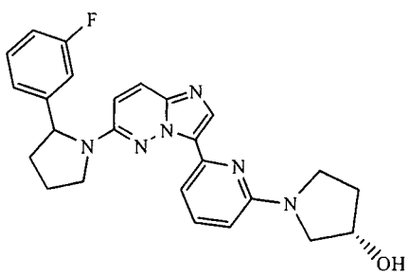
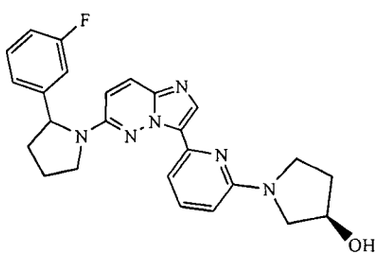
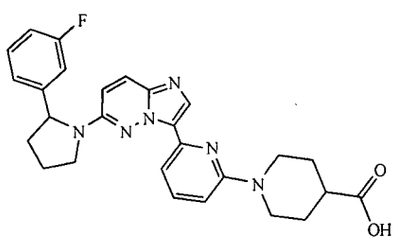
En el paso 5-2, se agregó 4-hidroxi-piperidina (30 miligramos, 0.30 milimoles) a una mezcla de 6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(6-fluoro-piridin-2-il)-imidazo-[1,2-b]-piridazina (40 miligramos, 0.13 milimoles), 12 miligramos de KF (0.30 milimoles) en 1.5 mililitros de sulfóxido de dimetilo (DMSO). La mezcla resultante se calentó a 110°C, y se agitó durante 8 horas a 110°C. El producto se purificó entonces utilizando LC/MS de preparación desencadenada por la masa, dando el 1-(6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol (5-2). ^{1}H RMN (400 MHz, D_3 acetonitrilo) δ ppm 8.35 (br s, 1H), 8.22 (app q, *J*= 6.1 Hz, 2H), 7.58 (br s, 1H), 7.42-7.02 (m, 4H), 6.82 (app d, *J*= 6.5 Hz, 1H), 5.42 (dd, *J*= 5.2, 1.4 Hz, 1H), 4.25-4.00 (m, 3H), 3.88-3.82 (m, 1H), 3.76 (app q, *J*= 6.4 Hz, 1H), 3.15 (app dd, *J*= 4.7, 2.2 Hz, 2H), 2.49-2.42 (m, 2H), 2.09-2.01 (m, 3H), 1.88-1.80 (m, 2H), 1.44 (app q, *J*= 7.4 Hz, 2H). LCMS observada m/z 477.2.

Mediante la repetición de los procedimientos descritos en los ejemplos anteriores, utilizando los materiales de partida apropiados, se obtuvieron los siguientes los compuestos de la fórmula (I), como

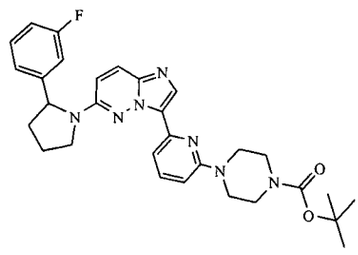
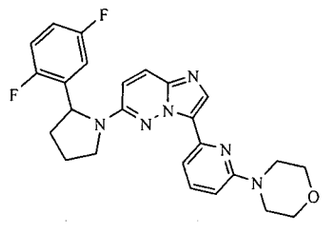
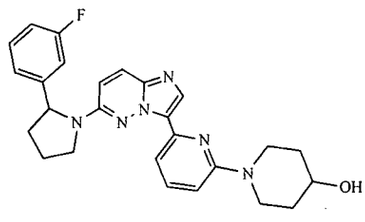
se identifican en la Tabla 4.

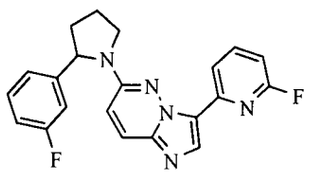
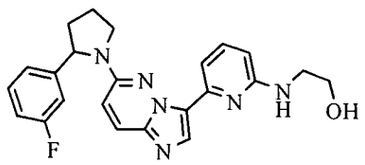
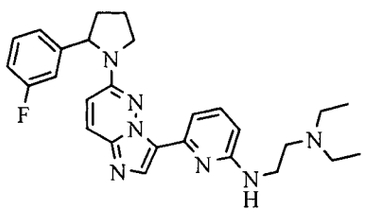
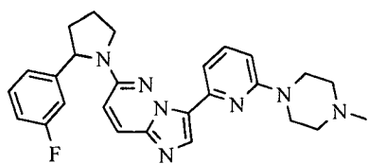
Tabla 4

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
1		*m/z* 462.2 (M+1)
2		*m/z* 476.3 (M+1)
3		*m/z* 476.3 (M+1)
4		*m/z* 477.3 (M+1)

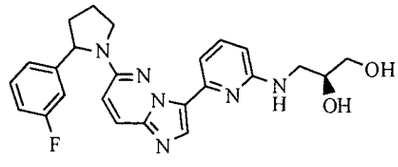
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
5		*m/z* 458.2 (M+1)
6		*m/z* 445.2 (M+1)
7		*m/z* 445.2 (M+1)
8		*m/z* 487.2 (M+1)

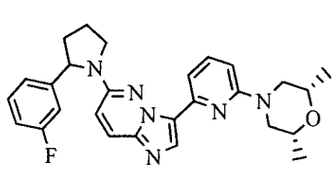
291

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
9		*m/z* 544.3 (M+1)
10		*m/z* 463.2 (M+1)
11		^{1}H RMN (DMSO-d6) 8.04 (s, 1 H), 7.88 (d, 1 H), 7.40-7.60 (m, 2 H), 7.37 (q, 1 H), 7.13-7.17 (m, 2 H), 7.00-7.05 (m, 1 H), 6.75-6.85 (bs, 1 H), 6.73 (d, 1 H), 5.15-5.17 (m, 1 H), 4.67 (d, 1 H), 4.04-4.10 (m, 2 H), 3.96-4.01 (m, 1 H), 3.64-3.71 (m, 2 H), 3.05-3.11 (m, 2 H), 2.00-2.06 (m, 2 H), 1.84-

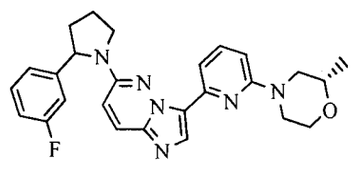
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1.89 (m, 1 H), 1.77-1.82 (m, 2 H), 1.33-1.40 (m, 2 H) *m/z* 473.2 (M+1)
12		*m/z* 378.4 (M+1)
13		*m/z* 419.5 (M+1)
14		*m/z* 474.6 (M+1)
15		^{1}H RMN (DMSO-d6) 8.10 (s, 1 H), 7.88 (d, 1 H), 7.46-7.66 (m, 2 H), 7.36-7.40 (m, 1 H), 7.12-7.18 (m, 2 H), 7.00-7.06 (m, 1

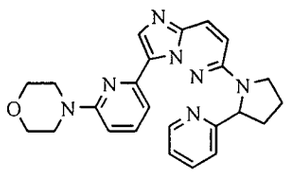
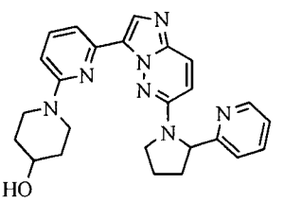
242

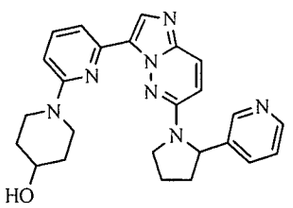
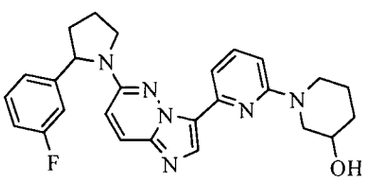
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		H), 6.80-6.90 (m, 1 H), 6.78 (d, 1 H), 5.14-5.18 (m, 1 H), 4.20 (d, 1 H), 4.11 (d, 1 H), 3.96-4.02 (m, 1 H), 3.50-3.90 (m, 4 H), 3.64-3.70 (m, 1 H), 3.32 (s, 3 H), 2.70-3.00 (m, 4 H), 2.45-2.50 (m, 1 H), 2.00-2.08 (m, 2 H), 1.84-1.91 (m, 1 H) *m/z* 458.5 (M+1)
16		^{1}H RMN (DMSO-d6) 8.03 (s, 1 H), 7.88 (d, 1 H), 7.26-7.44 (m, 3 H), 7.12-7.18 (m, 2 H), 7.01-7.06 (m, 1 H), 6.75-6.85 (m, 1 H), 6.50-6.56 (m, 1 H), 6.43 (d, 1 H), 5.14-5.18 (m, 1 H), 5.00-5.06 (bs, 1 H), 4.58-4.68 (m, 1 H),

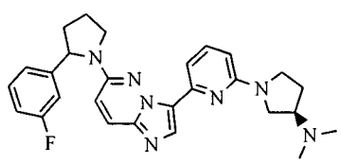
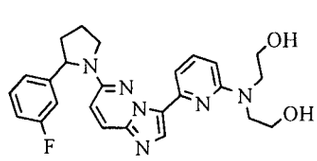
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		3.95-4.05 (m, 1 H), 3.62-3.70 (m, 2 H), 3.42-3.50 (m, 1 H), 3.36-3.38 (m, 2 H), 3.18-3.26 (m, 1 H), 2.45-2.50 (m, 1 H), 2.00-2.08 (m, 2 H), 1.82-1.90 (m, 1 H) *m/z* 449.5 (M+1)
17		^{1}H RMN (DMSO-d6) 8.10 (s, 1 H), 7.89 (d, 1 H), 7.42-7.60 (m, 2 H), 7.34-7.42 (m, 1 H), 7.12-7.18 (m, 2 H), 6.98-7.06 (m, 1 H), 6.76-6.86 (m, 1 H), 6.74 (d, 1 H), 5.14-5.19 (m, 1 H), 4.21 (d, 2 H), 3.96-4.02 (m, 1 H), 3.64-3.70 (m, 3 H), 2.45-2.50 (m, 1 H), 2.35-2.43 (m, 2 H), 1.98-2.08 (m, 2 H),

293

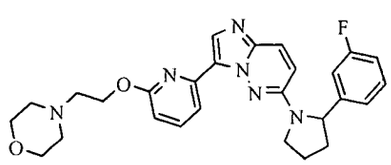
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1.82-1.90 (m, 1 H), 1.18 (m, 6 H) *m/z* 473.6 (M+1)
18		^{1}H RMN (DMSO-d6) 8.09 (s, 1 H), 7.89 (d, 1 H), 7.42-7.64 (m, 2 H), 7.33-7.42 (m, 1 H), 7.12-7.18 (m, 2 H), 6.98-7.06 (m, 1 H), 6.76-6.86 (m, 1 H), 6.73 (d, 1 H), 5.14-5.18 (m, 1 H), 4.20 (d, 1 H), 4.11 (d, 1 H), 3.95-4.05 (m, 1 H), 3.62-3.70 (m, 1 H), 3.50-3.62 (m, 2 H), 3.36-3.38 (m, 2 H), 2.74-2.84 (m, 1 H), 2.45-2.50 (m, 1 H), 1.98-2.07 (m, 2 H), 1.82-1.91 (m, 1 H), 1.18 (m, 3 H) *m/z* 459.5 (M+1)

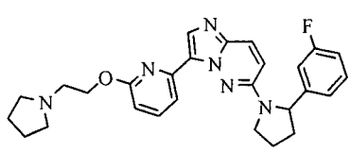
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
19		*m/z* 428.5 (M+1)
20		^{1}H RMN (DMSO-d6) 8.57 (d, 1 H), 8.03 (s, 1 H), 7.87 (d, 1 H), 7.67-7.71 (m, 1 H), 7.36-7.48 (bs, 2 H), 7.29 (d, 1 H), 7.20-7.23 (m, 1 H), 6.78-6.88 (bs, 1 H), 6.71 (d, 1H), 5.16-5.19 (q, 1 H), 4.65-4.68 (d, 1 H), 4.04-4.09 (m, 2H), 3.94-3.98 (m, 1 H), 3.65-3.73 (m, 2 H), 3.04-3.11 (m, 2 H), 2.45-2.48 (m, 1 H), 2.03-2.08 (m, 2 H), 1.95-2.01 (m, 1 H), 1.76-1.82 (m, 2 H), 1.33-1.40 (m, 2 H) *m/z* 442.5 (M+1)

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
21		*m/z* 442.5 (M+1)
22		^{1}H RMN (DMSO-d6) 8.06 (s, 1 H), 7.88 (d, 1 H), 7.40-7.50 (m, 2 H), 7.35-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.01-7.05 (m, 1 H), 6.75-6.85 (bs, 1 H), 6.69 (d, 1 H), 5.14-5.18 (q, 1 H), 4.83 (t, 1 H), 4.24-4.29 (m, 1H), 3.95-4.05 (m, 2 H), 3.63-3.70 (m, 1 H), 3.44-3.53 (m, 1 H), 2.87-2.93 (m,1 H), 2.67-2.73 (q, 1 H), 2.45-2.50 (m, 1 H), 2.00-2.06 (m, 2 H), 1.84-1.94 (m, 2 H), 1.70-1.76 (m, 1 H), 1.33-1.40 (m, 2 H)

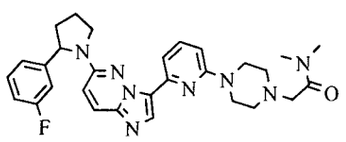
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		m/z 459.5 (M+1)
23		^{1}H RMN (DMSO-d6) 8.07 (s, 1 H), 7.87 (d, 1 H), 7.32-7.60 (m, 3 H), 7.11-7.19 (m, 2 H), 7.00-7.05 (m, 1 H), 6.75-6.85 (bs, 1 H), 6.36 (d, 1 H), 5.15-5.18 (m, 1 H), 3.96-4.01 (m, 1 H), 3.60-3.75 (m, 3 H), 3.33-3.37 (m, 1 H), 3.10-3.15 (m, 1 H), 2.73-2.80 (m, 1 H), 2.45-2.50 (m, 1 H), 2.11-2.18 (m, 1 H), 2.00-2.06 (m, 2 H), 1.84-1.90 (m, 1 H), 1.76-1.82 (m, 1 H) *m/z* 472.6 (M+1)
24		^{1}H RMN (DMSO-d6) 8.58 (d, 1 H), 8.41-8.43 (q, 1H), 8.02 (s, 1 H), 7.89 (d, 1

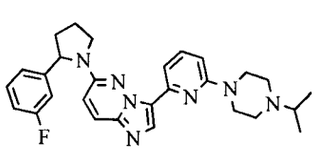
295

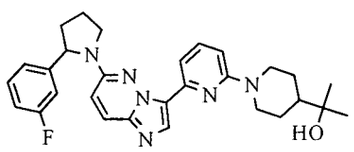
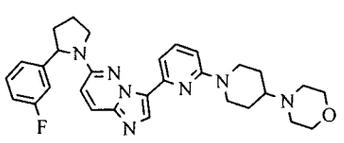
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		H), 7.68-7.71 (m, 1 H), 7.39-7.45 (m, 2 H), 7.32-7.35 (q, 1 H), 6.82-6.90 (bs, 1 H), 6.72 (d, 1H), 5.19-5.23 (q, 1 H), 4.67 (d, 1 H), 4.03-4.09 (m, 2 H), 3.97-4.02 (m, 1 H), 3.65-3.71 (m, 2 H), 3.05-3.10 (m, 2 H), 2.51-2.53 (m, 1 H), 2.01-2.09 (m, 2 H), 1.85-1.91 (m, 1 H), 1.76-1.82 (m, 2 H), 1.31-1.40 (m, 2 H) *m/z* 463.5 (M+1)
25		^{1}H RMN (DMSO-d6) 8.58 (d, 1 H), 8.41-8.43 (q, 1H), 8.02 (s, 1 H), 7.89 (d, 1 H), 7.68-7.71 (m, 1 H), 7.39-7.45 (m, 2 H), 7.32-7.35 (q, 1 H), 6.82-6.90

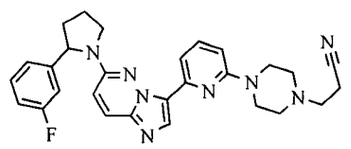
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(bs, 1 H), 6.72 (d, 1H), 5.19-5.23 (q, 1 H), 4.67 (d, 1 H), 4.03-4.09 (m, 2 H), 3.97-4.02 (m, 1 H), 3.65-3.71 (m, 2 H), 3.05-3.10 (m, 2 H), 2.51-2.53 (m, 1 H), 2.01-2.09 (m, 2 H), 1.85-1.91 (m, 1 H), 1.76-1.82 (m, 2 H), 1.31-1.40 (m, 2 H) *m/z* 489.6 (M+1)
26		^{1}H RMN (DMSO-d6) 8.13 (s, 1 H), 7.92 (d, 1 H), 7.74-7.98 (bs, 1 H), 7.68-7.66 (bs, 1 H), 7.36-7.40 (m, 1 H), 7.14-7.20 (m, 2 H), 7.00-7.06 (m, 1 H), 6.80-6.92 (bs, 1 H), 6.70 (d, 1H), 5.16-5.20 (q, 1 H), 4.47-4.56 (m, 2 H), 3.98-

296

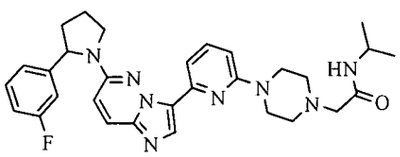
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		4.03(m, 1 H), 3.65-3.71 (m, 1 H), 3.03-3.20 (m, 2 H), 2.70-2.95 (m,4 H), 2.45-2.50 (m, 1 H), 2.00-2.08 (m, 2 H), 1.85-1.90 (m, 1 H), 1.71-1.83 (m, 4 H) *m/z* 473.6 (M+1)
27		^{1}H RMN (DMSO-d6) 8.06 (s, 1 H), 7.88 (d, 1 H), 7.42-7.60 (m, 2 H), 7.34-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.00-7.05 (m, 1 H), 6.75-6.85 (bs, 1 H), 6.73 (d, 1H), 5.14-5.19 (q, 1 H), 3.96-4.01 (m, 1 H), 3.64-3.70 (q, 1 H), 3.48-3.58 (bs, 4 H), 3.15-3.24 (bs, 2 H), 3.04 (s, 3H), 2.82 (s, 3 H), 2.50-2.60

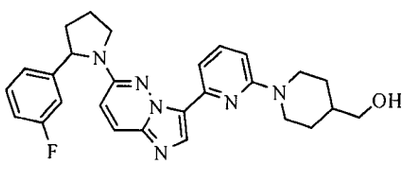
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(bs, 4 H), 2.45-2.50 (m, 1 H), 2.01-2.06 (m, 2 H), 1.84-1.89 (m, 1 H) *m/z* 529.6 (M+1)
28		^{1}H RMN (DMSO-d6) 8.05 (s, 1 H), 7.88 (d, 1 H), 7.42-7.60 (m, 2 H), 7.35-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.00-7.05 (m, 1 H), 6.76-6.86 (bs, 1 H), 6.71 (d, 1H), 5.15-5.17 (q, 1 H), 3.96-4.01 (m, 1 H), 3.64-3.70 (q, 1 H), 3.46-3.54 (bs, 4 H), 2.64-2.71 (m, 1 H), 2.50-2.56 (bs, 4 H), 2.45-2.50 (m, 1 H), 2.00-2.06 (m, 2 H), 1.84-1.90 (m, 1 H), 1.00 (d, 6 H) *m/z* 486.6 (M+1)

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
29		^{1}H RMN (DMSO-d6) 8.04 (s, 1 H), 7.88 (d, 1 H), 7.34-7.50 (m, 3 H), 7.12-7.37 (m, 2 H), 7.00-7.16 (m, 1 H), 6.76-6.84 (bs, 1H), 6.72 (d, 1H), 5.15-5.18 (q, 1 H), 4.45 (d, 1 H), 4.01 (s, 1 H), 3.96-4.01 (m, 1 H), 3.64-3.68 (m, 1 H), 2.65-2.71 (m, 2 H), 2.44-2.48 (m, 1 H), 2.00-2.06 (m, 2 H), 1.84-1.89 (m, 1 H), 1.74-1.79 (m, 2 H), 1.38-1.45 (m, 1 H), 1.18-1.28 (m, 2 H), 1.04 (s, 6 H), 0.82-.088 (m, 1H) *m/z* 501.6 (M+1)
30		^{1}H RMN (DMSO-d6) 8.04 (s, 1 H), 7.87 (d, 1 H), 7.40-7.52 (m, 2 H), 7.34-

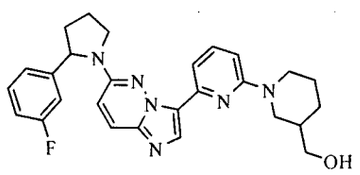
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.00-7.05 (m, 1 H), 6.77-6.85 (bs, 1H), 6.74 (d, 1H), 5.14-5.18 (q, 1 H), 4.36 (d, 2 H), 3.96-4.01 (m, 1 H), 3.63-3.69 (q, 1 H), 3.55 (t, 4 H), 2.80 (t, 2 H), 2.42-2.50 (m, 5 H), 2.34-2.40 (m, 1 H), 2.00-2.05 (m, 2 H), 1.82-1.89 (m, 3 H), 1.33-1.41 (m, 2 H) *m/z* 528.6 (M+1)
31		^{1}H RMN (DMSO-d6) 8.06 (s, 1 H), 7.88 (d, 1 H), 7.41-7.60 (m, 2 H), 7.34-7.40 (m, 1 H), 7.12-7.18 (m, 2 H), 7.00-7.15 (m, 1 H), 6.77-6.85 (bs, 1H), 6.74 (d, 1H), 5.15-5.18 (q,

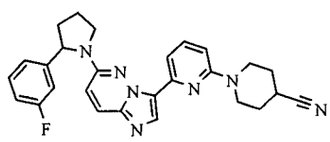
298

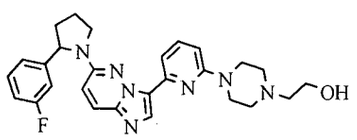
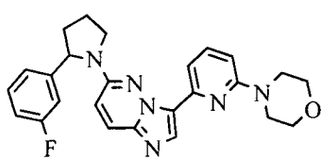
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1 H), 3.96-4.01 (m, 1 H), 3.64-3.70 (q, 1 H), 3.54 (t, 4 H), 2.72 (t, 2 H), 2.62 (t, 2 H), 2.51-2.55 (m, 4 H), 2.45-2.50 (m, 1 H), 2.00-2.06 (m, 2 H), 1.84-1.90 (m, 1 H) *m/z* 497.6 (M+1)
32		^{1}H RMN (DMSO-d6) 8.07 (s, 1 H), 7.88 (d, 1 H), 7.50-7.58 (bs, 1 H), 7.42-7.48 (bs, 1 H), 7.35-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.01-7.05 (m, 1 H), 6.78-6.85 (bs, 1 H), 6.73 (d, 1H), 5.15-5.18 (q, 1 H), 3.96-4.01 (m, 1 H), 3.87-3.94 (m, 1 H), 3.64-3.70 (m, 1 H), 3.54-360 (bs, 4 H), 2.91-2.96 (bs, 2 H),

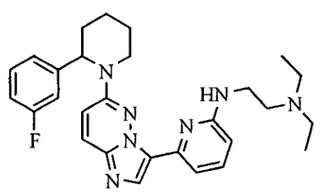
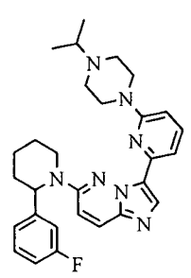
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2.50-2.60 (bs, 4 H), 2.45-2.50 (m, 1 H), 2.00-2.06 (m, 2 H), 1.84-1.90 (m, 1 H), 1.08 (d, 6 H) *m/z* 543.7 (M+1)
33		^{1}H RMN (DMSO-d6) 8.04 (s, 1 H), 7.87 (d, 1 H), 7.40-7.50 (m, 2 H), 7.35-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.01-7.05 (m, 1 H), 6.76-6.85 (bs, 1H), 6.72 (d, 1H), 5.14-5.17 (q, 1 H), 4.46 (t, 1 H), 4.37 (d, 2 H), 3.96-4.01 (m, 1 H), 3.64-3.69 (q, 1 H), 3.27 (t, 2 H), 2.74-2.81 (m, 2 H), 2.45-2.50 (m, 1 H), 2.00-2.06 (m, 2 H), 1.84-1.89 (m, 1 H), 1.58-1.64 (m, 1 H), 1.08-1.17 (m, 2 H)

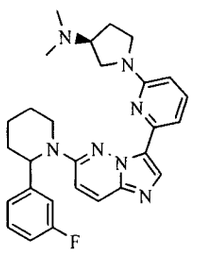
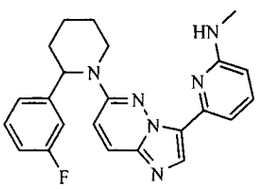
299

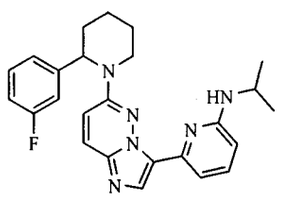
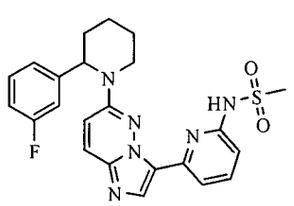
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		m/z 473.6 (M+1)
34		^{1}H RMN (DMSO-d6) 8.05 (s, 1 H), 7.88 (d, 1 H), 7.40-7.50 (m, 2 H), 7.34-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.00-7.05 (m, 1 H), 6.76-6.85 (bs, 1H), 6.69 (t, 1 H), 5.15-5.18 (q, 1 H), 4.54-4.57 (m, 1 H), 4.34 (d, 1 H), 4.22 (d, 1 H), 3.96-4.02 (m, 1 H), 3.64-3.70 (q, 1 H), 3.28-3.37 (m, 2 H), 2.81-2.88 (m, 1 H), 2.59 (t, 1 H), 2.45-2.50 (m, 1 H), 2.00-2.08 (m, 2 H), 1.84-1.90 (m, 1 H), 1.72-1.77 (m, 1 H), 1.66-1.72 (m, 1 H), 1.58-1.65 (m, 1 H), 1.40-1.59 (m, 1 H), 1.14-1.22

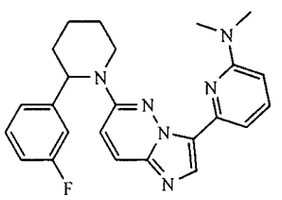
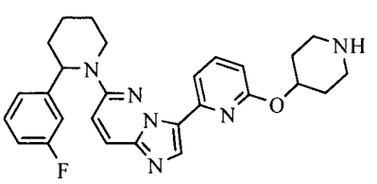
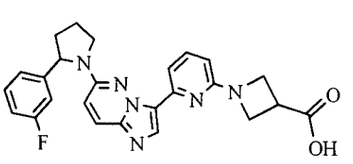
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(m, 1 H) *m/z* 473.6 (M+1)
35		^{1}H RMN (DMSO-d6) 8.07 (s, 1 H), 7.88 (d, 1 H), 7.41-7.60 (m, 2 H), 7.34-7.40 (m, 1 H), 7.12-7.18 (m, 2 H), 7.00-7.15 (m, 1 H), 6.78-6.85 (bs, 1H), 6.77 (d, 1H), 5.15-5.18 (q, 1 H), 3.96-4.01 (m, 1 H), 3.83-3.89 (m, 2 H), 3.64-3.70 (q, 1 H), 3.09-3.14 (m, 1 H), 2.45-2.50 (m, 1 H), 2.00-2.06 (m, 2 H), 1.94-1.97 (m, 2 H), 1.84-1.89 (m, 1 H), 1.71-1.77 (m, 2 H) *m/z* 468.5 (M+1)

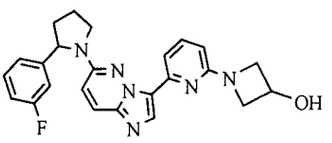
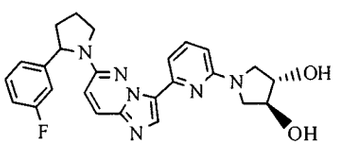
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
36		^{1}H RMN (DMSO-d6) 8.05(s, 1 H), 7.88 (d, 1 H), 7.42-7.60 (m, 2 H), 7.35-7.40 (m, 1 H), 7.13-7.17 (m, 2 H), 7.00-7.05 (m, 1 H), 6.75-6.85 (bs, 1H), 6.72 (d, 1H), 5.14-5.18 (q, 1 H), 4.43 (t, 1 H), 3.96-4.01 (m, 1 H), 3.63-3.70 (q, 1 H), 3.47-3.57 (m, 6 H), 2.50-2.55 (m, 4 H), 2.40-2.50 (m, 3 H), 2.00-2.06 (m, 2 H), 1.84-1.89 (m, 1 H) *m/z* 488.6 (M+1)
37		^{1}H RMN (DMSO-d6) δ 8.07 (s, 1 H), 7.88 (d, 1 H), 7.46-7.68 (m, 2 H), 7.36-7.40 (q, 1 H), 7.12-7.18 (m, 2 H), 7.00-7.06 (m, 1

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		H), 6.78-6.88 (bs, 1 H), 6.73 (d, 1 H), 5.15-5.18 (q, 1 H), 3.96-4.01 (m, 1 H), 3.70-3.73 (m, 4 H), 3.64-3.69 (q, 1 H), 3.46-3.51 (m, 4 H), 2.45-2.50 (m, 1 H), 2.01-2.06 (m, 2 H), 1.84-1.89 (m, 1 H) *m/z* 445.5 (M+1)
38		*m/z* 488.3 (M+1)
39		*m/z* 500.3 (M+1)

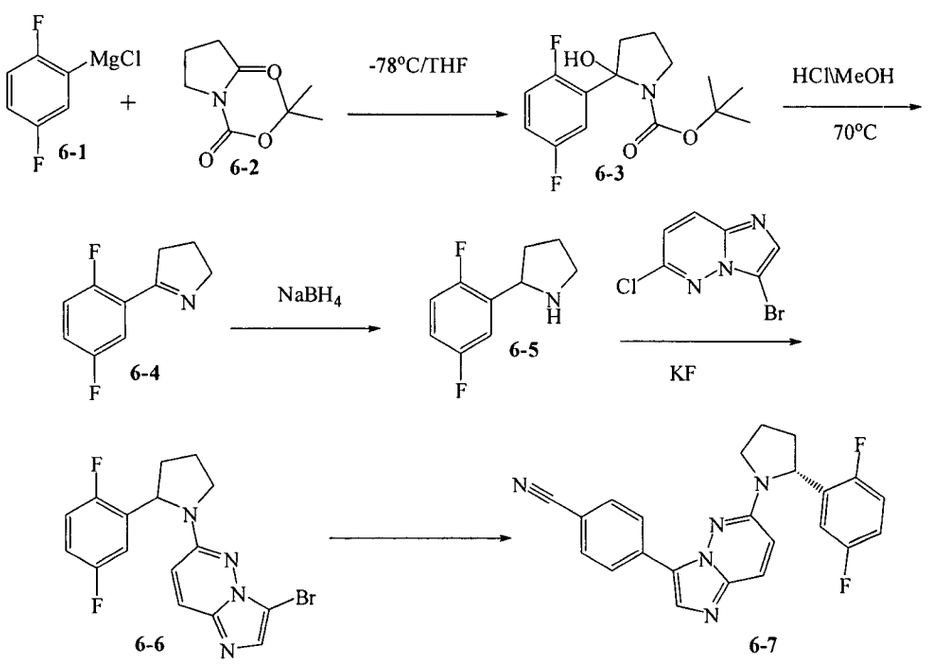
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
40		*m/z* 486.3 (M+1)
41		^{1}H RMN (DMSO-d6): d 8.06 (s, 1 H), 7.75 (s, 1 H), 7.51 (d, 1 H), 7.32-7.40 (m, 2 H), 7.22 (d, 1 H), 7.14 (d, 2 H), 6.99-7.05 (m, 1 H), 6.45-6.50 (m, 1 H), 6.35 9d, 1 H), 4.14-4.21 (m, 1 H), 3.30-3.39 (m, 2 H), 2.82 (d, 3 H), 2.17-2.26 (m, 1 H), 2.00-2.10 (m, 1 H), 1.56-1.83 (m, 3 H), 1.35-1.50 (m, 1 H) *m/z* 403.2 (M+1)

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
42		^{1}H RMN (DMSO-d6): d 8.02 (s, 1 H), 7.90 (d, 1 H), 7.46 (d, 1 H), 7.30-7.40 (m, 2 H), 7.21 (d, 1 H), 7.13 (d, 2 H), 6.98-7.06 (m, 1 H), 6.30-6.36 (m, 2 H), 4.12-4.20 (m, 1 H), 4.02-4.10 (m, 1 H), 3.30-3.38 (m, 2 H), 2.18-2.26 (m, 1 H), 2.00-2.10 (m, 1 H), 1.56-1.84 (m, 3 H), 1.36-1.48 (m, 1 H), 1.17 (d, 6 H) *m/z* 431.2 (M+1)
43		^{1}H RMN (DMSO-d6): d 10.63 (s, 1 H), 8.06 (s, 1 H), 7.97 (s, 1 H), 7.94 (d, 1 H), 7.72 (t, 1 H), 7.33-7.40 (m, 1 H), 7.25 (d, 1 H), 7.12-7.18 (m, 2 H),

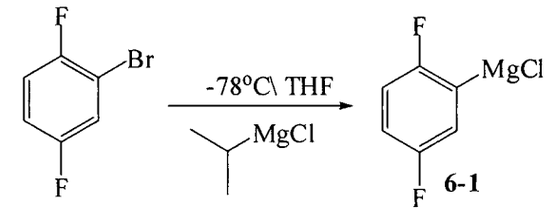
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		6.99-7.05 (m, 1 H), 6.80 (d, 1 H), 4.15-4.22 (m, 1 H), 3.42 (s, 3 H), 3.35-3.42 (m, 2 H), 2.17-2.26 (m, 1 H), 2.01-2.14 (m, 1 H), 1.57-1.85 (m, 3 H), 1.36-1.49 (m, 1 H) *m/z* 467.2 (M+1)
44		*m/z* 417.3 (M+1)
45		*m/z* 473.3 (M+1)
46		*m/z* 459.2 (M+1)

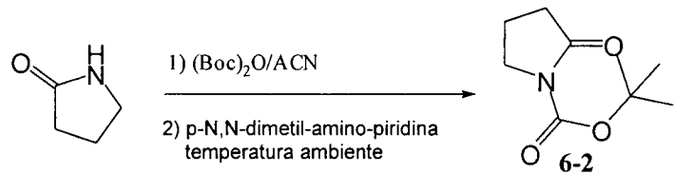
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
47		*m/z* 431.1 (M+1)
48		*m/z* 461.5 (M+1)

Esquema 6A



Esquema 6B





Ejemplo 6

(R)-4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo

El (R)-4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo (7-7) se sintetizó a partir de cloruro de (2,5-difluoro-fenil)-magnesio (6-1), y 2-oxo-pirrolidin-1-carboxilato de terbutilo (7-2) en cinco pasos, como se muestra en el esquema 6A. Se sintetizaron el cloruro de (2,5-difluoro-fenil)-magnesio (7-1), y el 2-oxo-pirrolidin-1-carboxilato de terbutilo (7-2) como se muestra en el esquema de reacción 6B.

Para sintetizar el cloruro de (2,5-difluoro-fenil)-magnesio (6-1), una solución de 2-bromo-1,4-difluoro-benceno (10 gramos, 52 milimoles) en 30 mililitros de tetrahidrofurano anhidro se enfrió a -78°C bajo argón, y entonces se agregaron por goteo 27 mililitros de cloruro de isopropil-magnesio en tetrahidrofurano (2.0 M, 54

milimoles). La mezcla de reacción se calentó entre -20°C y -30°C durante 30 minutos, y entonces se enfrió a -78°C para utilizarse en la síntesis del 2-(2,5-difluoro-fenil)-2-hidroxi-pirrolidin-1-carboxilato de terbutilo (6-3) sin mayor purificación.

Para sintetizar el 2-oxo-pirrolidin-1-carboxilato de terbutilo (7-2), se agregó p-N,N-dimetil-amino-piridina (0.7 gramos, 5.9 milimoles), a temperatura ambiente, a una solución de 2-pirrolidona (5 gramos, 59 milimoles), y dicarbonato de diterbutilo (26 gramos, 118 milimoles) en 100 mililitros de acetonitrilo. La mezcla de reacción se agitó durante 3 horas, y el acetonitrilo se removió utilizando un evaporador giratorio, lo cual dio como resultado un residuo color naranja claro. El residuo se reconstituyó en acetato de etilo (300 mililitros), y la capa orgánica se lavó con salmuera (150 mililitros, 3 veces). La capa orgánica se secó con sulfato de sodio, y el acetato de etilo se removió utilizando un evaporador giratorio, lo cual dio como resultado el 2-oxo-pirrolidin-1-carboxilato de terbutilo (6-2) como un residuo color naranja claro.

En el paso 6A-1, se agregó por goteo cloruro de (2,5-difluoro-fenil)-magnesio (6-1), a una solución de 2-oxo-pirrolidin-1-carboxilato de terbutilo (6-2) (9.6 gramos, 52 milimoles) en tetrahidrofurano bajo argón a -78°C. Se utilizaron alícuotas de máximo 5 mililitros para minimizar el aumento de temperatura del reactivo de cloruro de magnesio. La solución resultante se agitó entonces a -78°C durante una hora. La solución entonces se calentó a temperatura ambiente, y se apagó con HCl concentrado (4 mililitros). Entonces se removió el

solvente utilizando un evaporador giratorio, lo cual dio como resultado un residuo amarillo claro. Entonces el residuo se reconstituyó en acetato de etilo y se extrajo con salmuera (150 mililitros, 3 veces). La capa orgánica se secó entonces utilizando sulfato de sodio. El acetato de etilo se removió, proporcionando el 2-(2,5-difluoro-fenil)-2-hidroxi-pirrolidin-1-carboxilato de terbutilo (6-3) como un aceite amarillo claro. m/z = 300 [M+1] El producto se utilizó sin mayor purificación.

En el paso 6A-2, se agregó ácido clorhídrico concentrado (23 mililitros, 260 milimoles) a una solución de 2-(2,5-difluoro-fenil)-2-hidroxi-pirrolidin-1-carboxilato de terbutilo (6-3) (15.6 gramos, 52 milimoles) en metanol. La mezcla de reacción se calentó a 70°C mientras se agitaba, y luego se agitó a 70°C durante 6 horas. La mezcla de reacción se enfrió a temperatura ambiente, y se neutralizó con una solución de hidróxido de sodio 7.5 M (35 mililitros, 263 milimoles). El metanol se removió y la pasta acuosa resultante se reconstituyó con acetato de etilo (250 mililitros). La capa orgánica se lavó con salmuera (150 mililitros, 3 veces), y entonces se secó con sulfato de sodio. Luego el acetato de etilo se removió para proporcionar el 5-(2,5-difluoro-fenil)-3,4-dihidro-2H-pirrol (6-4) como un aceite amarillo claro. m/z = 182.2 [M+1].

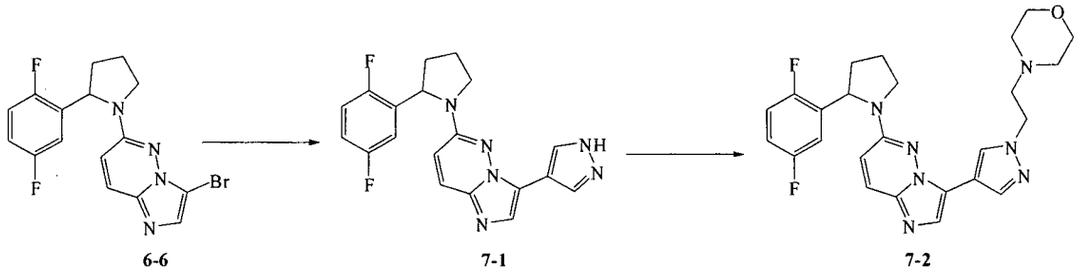
En el paso 6A-3, se agregó borohidruro de sodio (2.1 gramos, 55.2 milimoles) a temperatura ambiente a una solución de 5-(2,5-difluoro-fenil)-3,4-dihidro-2H-pirrol (6-4) (5.0 gramos, 28 milimoles) en etanol anhidro (150 mililitros). La mezcla de reacción se agitó

durante la noche a temperatura ambiente. El etanol se removió utilizando un evaporador giratorio, y el sólido color naranja resultante se reconstituyó con acetato de etilo. La capa orgánica se lavó con salmuera (150 mililitros, 3 veces), se secó con sulfato de sodio y el acetato de etilo se removió para proporcionar la 2-(2,5-difluoro-fenil)-pirrolidina (6-5) como un aceite amarillo claro. m/z = 184.2 [M+1].

En el paso 6A-4, se agregó 2-(2,5-difluoro-fenil)-pirrolidina (6-5) (1.7 gramos, 9.3 milimoles) a una solución de 3-bromo-6-cloro-imidazo-[1,2-b]-piridazina (11-1) (1.1 gramos, 230.92), y fluoruro de potasio (2.7 gramos, 46 milimoles) en sulfóxido de dimetilo (10 mililitros). La solución resultante se calentó a 130°C, y se agitó durante la noche. La pasta acuosa color naranja oscuro resultante se enfrió a temperatura ambiente, se vertió en 50 mililitros de agua desionizada, y se extrajo con acetato de etilo (150 mililitros, 3 veces). El acetato de etilo se secó con sulfato de sodio, y luego se removió para proporcionar un sólido color naranja. Este sólido se reconstituyó con cantidades mínimas de dicloro-metano (DCM), y se purificó utilizando una columna de gel de sílice (40 gramos, ISCO), y un gradiente del 0 al 5 por ciento de metanol:DCM durante un periodo de 20 minutos, seguido por metanol al 5 por ciento durante 10 minutos adicionales. El solvente se removió a partir de las fracciones deseadas para proporcionar la 3-bromo-6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina (6-6) como un sólido amarillo claro. m/z = 379.2 [M+1].

En el paso 6A-5, se agregó paladio-tetraquis (25 miligramos, 0.02 milimoles) a una solución de 3-bromo-6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina (6-6) (77 miligramos, 0.23 milimoles), carbonato de sodio (85 miligramos, 0.81 milimoles), y ácido 4-ciano-fenil-borónico (60 miligramos, 0.41 milimoles) en 2 mililitros de dioxano y 0.5 mililitros de agua contenida en un tubo de reacción de microondas. La solución resultante se calentó en un reactor de microondas durante 25 minutos a 150°C, y la pasta acuosa amarilla se enfrió a temperatura ambiente, y se filtró a través de una frita de nylon de 0.2 micras. El solvente se removió a partir del licor madre, y el residuo restante se reconstituyó en metanol y además se purificó mediante LC/MS de preparación. Las fracciones deseadas se secaron para proporcionar el producto deseado como una mezcla racémica, la cual entonces se purificó mediante LC quiral para proporcionar el (R)-4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo (6-7) como un sólido blanco puro quiral junto con el (S)-4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo como un sólido blanco puro quiral.

Esquema 7



Ejemplo 7

4-(2-(4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-1H-pirazol-1-il)-etil)-morfolina

La 4-(2-(4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-1H-pirazol-1-il)-etil)-morfolina (7-2) se sintetizó en dos pasos como se muestra en el esquema 7.

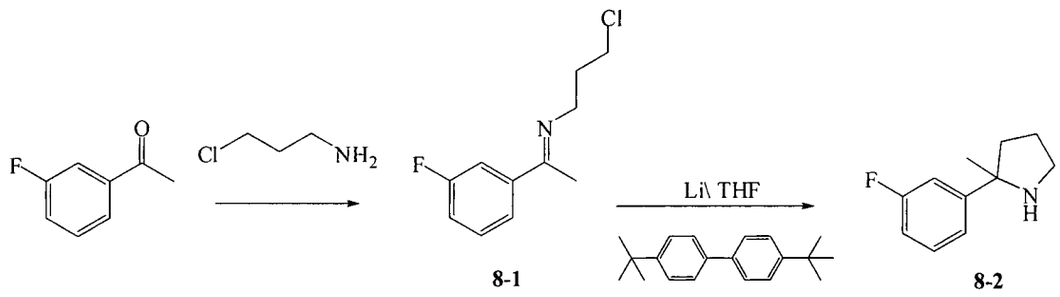
En el paso 7-1, se agregaron $[Pd(dppf)_2]Cl_2$ (54 miligramos, 0.07 milimoles) en 2.5 mililitros de 1,4-dioxano y 0.5 mililitros de agua a una solución de 3-bromo-6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina (6-6) (0.25 gramos, 0.7 milimoles), carbonato de sodio (0.25 gramos, 2.5 milimoles), y 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (0.27 gramos, 1.4 milimoles) contenidos en un tubo de reacción de microondas. La mezcla de reacción se calentó en el reactor de microondas durante veinte minutos a 150°C, y la pasta acuosa amarilla se enfrió entonces a temperatura ambiente, y se filtró a través de una frita de nylon de 0.2 micras. El solvente se removió a partir del licor madre, y el residuo restante se reconstituyó en dicloro-metano (DCM). Esta solución se cargó en una columna de 12 gramos de gel de sílice, y se eluyó utilizando un gradiente del 0 al 5 por ciento de metanol en dicloro-metano durante 30 minutos. El solvente se removió a partir de las fracciones deseadas, para proporcionar la 6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(1H-pirazol-4-il)-imidazo-[1,2-b]-piridazina (7-1) como un sólido grisáceo. m/z = 367.4 [M+1].

En el paso 7-2, se agregó clorhidrato de 4-(2-cloro-etil)-

306

morfolina (40 miligramos, 0.2 milimoles) a una solución de 6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(1H-pirazol-4-il)-imidazo-[1,2-b]-piridazina (7-1) (35 miligramos, 0.1 milimoles), y carbonato de cesio (100 miligramos, 0.35 milimoles) en N,N-dimetil-formamida (5 mililitros). La mezcla de reacción se agitó a temperatura ambiente durante la noche, y luego se removió la dimetil-formamida utilizando un evaporador giratorio. El residuo resultante se reconstituyó en acetato de etilo (30 mililitros), y la capa orgánica se extrajo con salmuera, y entonces se secó utilizando sulfato de sodio. El acetato de etilo se removió, y el producto además se purificó mediante LC/MS de preparación, para proporcionar la 4-(2-(4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-1H-pirazol-1-il)-etil)-morfolina (7-2) como un sólido blanco. m/z = 480.2 [M+1].

Esquema 8



8-1 8-2

Ejemplo 8

2-(3-fluoro-fenil)-2-metil-pirrolidina

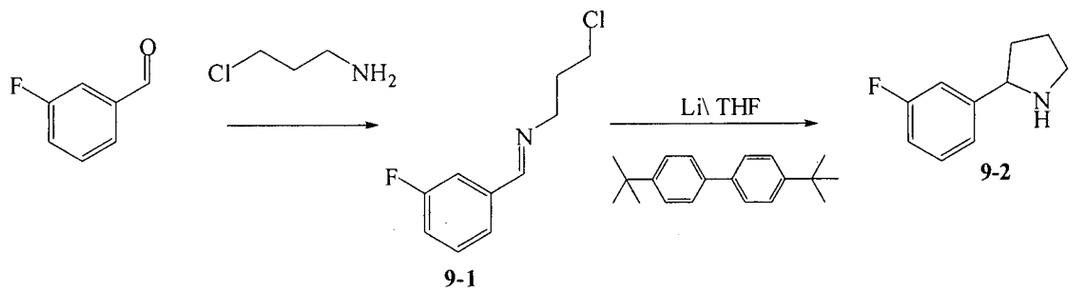
La 2-(3-fluoro-fenil)-2-metil-pirrolidina (8-2) se sintetizó en dos pasos como se muestra en el esquema 8.

En el paso 8-1, se agregó clorhidrato de 3-cloro-propan-1-amina (4.1 gramos, 32 milimoles) a una suspensión de 1-(3-fluoro-fenil)-etanona (4.4 gramos, 32 milimoles), y carbonato de sodio (3.7 gramos, 35 milimoles) en agua (15 mililitros). La mezcla de reacción se agitó durante la noche, y la solución resultante entonces se extrajo con acetato de etilo (150 mililitros, 3 veces). La capa orgánica se secó con sulfato de sodio, y se removió el acetato de etilo, para proporcionar la 3-cloro-N-(1-(3-fluoro-fenil)-etiliden)-propan-1-amina (8-1) como un aceite amarillo claro. m/z = 214.0 [M+1].

En el paso 8-2, se agregó 3-cloro-N-(1-(3-fluoro-fenil)-etiliden)-propan-1-amina (8-1) (4.7 gramos, 22 milimoles), a -78°C a una solución de gránulos de litio (0.8 gramos, 110 milimoles), y 4,4'-diterbutil-bifenilo (0.6 gramos, 2.2 milimoles) en tetrahidrofurano (40 mililitros) enfriada hasta -78°C. La solución resultante se agitó a -78°C durante 2 horas, entonces se apagó con agua, y la temperatura se permitió aumentar a 20°C. Luego los sólidos se removieron mediante filtración, el licor madre se redujo utilizando un evaporador giratorio, y el residuo resultante se reconstituyó en acetato de etilo. El orgánico se lavó con HCl 1N (25 mililitros, 3 veces), y la capa acuosa se extrajo con acetato de etilo. La capa acuosa se neutralizó con una solución de NaOH 1N, y se extrajo con acetato de etilo (100 mililitros, 3 veces). La capa orgánica se secó con sulfato de sodio, y el solvente se removió, para proporcionar la 2-(3-fluoro-fenil)-2-metil-pirrolidina (8-2) como un aceite amarillo

claro. m/z = 180.3 [M+1].

Esquema 9



Ejemplo 9

2-(3-fluoro-fenil)-pirrolidina

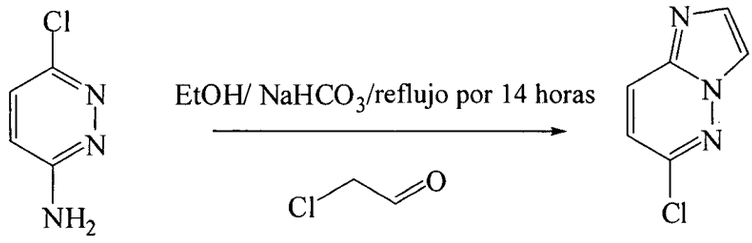
La 2-(3-fluoro-fenil)-pirrolidina (9-2) se sintetizó en dos pasos como se muestra en el esquema 9.

En el paso 9-1, se agregó clorhidrato de 3-cloro-propan-1-amina (43 gramos, 331 milimoles) a una suspensión de 3-fluoro-benzaldehído (41 gramos, 331 milimoles), y carbonato de sodio (39 gramos, 364 milimoles) en agua (100 mililitros), y la pasta acuosa resultante se agitó durante la noche. La solución resultante se extrajo con acetato de etilo (150 mililitros, 3 veces) y la capa orgánica se secó con sulfato de sodio. El acetato de etilo se removió para proporcionar la 3-cloro-N-(3-fluoro-benciliden)-propan-1-amina (9-1) como un aceite amarillo claro m/z = 200.0 [M+1].

En el paso 9-2, se agregó 3-cloro-N-(3-fluoro-benciliden)-propan-1-amina (9-1) (53 gramos, 266 milimoles), a -78°C, a una solución de gránulos de litio (5.5 gramos, 800 milimoles), y 4,4'-diterbutil-bifenilo (5.7 gramos, 21 milimoles) en tetrahidrofurano (50

mililitros) enfriada hasta -78°C. La solución resultante se agitó a -78°C durante 2 horas, entonces se apagó con agua, y la temperatura se permitió elevarse hasta 20°C. Los sólidos se removieron mediante filtración, y el licor madre se redujo utilizando un evaporador giratorio. El residuo resultante se reconstituyó en acetato de etilo, el orgánico se lavó con HCl 1N (25 mililitros, 3 veces), y la capa acuosa se extrajo con acetato de etilo. La capa acuosa entonces se neutralizó con una solución de NaOH 1N, y la capa acuosa se extrajo con acetato de etilo (100 mililitros, 3 veces). La capa orgánica se secó con sulfato de sodio, y el solvente se removió para proporcionar la 2-(3-fluoro-fenil)-pirrolidina (9-2) como un aceite amarillo claro. m/z = 165.2 [M+1].

Esquema 10



10-1

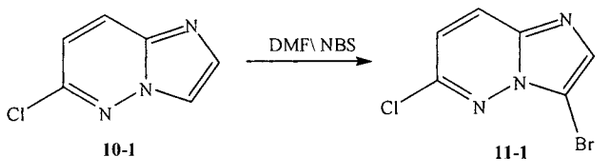
Ejemplo 10

Cloro-imidazo-[1,2-b]-piridazina

La cloro-imidazo-[1,2-b]-piridazina (10-1) se sintetizó como se muestra en el esquema 10, en donde se agregó cloro-acetaldehído (al 55 por ciento en agua, 126 mililitros, 880 milimoles) a una solución de 6-cloro-piridazin-3-il-amina (25.43 gramos, 196 milimoles), y $NaHCO_3$ (28 gramos, 334 milimoles) en EtOH (600

mililitros), y entonces la mezcla de reacción se calentó a reflujo mientras se agitaba durante 14 horas. Entonces la mezcla de reacción color café oscuro resultante se concentró al vacío, y el residuo resultante se reconstituyó con dicloro-metano (DCM). Esta solución se filtró a través de un cojín de Celite, y el sólido se lavó con dicloro-metano, y entonces se removió el solvente para proporcionar un aceite color café oscuro. Se agregaron HCl 2M (290 mililitros) y agua (300 mililitros) al residuo, y la pasta acuosa resultante se agitó a temperatura ambiente durante 15 minutos. La solución se filtró a través de un cojín de Celite, y la torta del filtro se lavó con agua. El filtrado se extrajo con dietil-éter (200 mililitros, 3 veces). La capa acuosa se enfrió a 0°C (baño helado), y se neutralizó utilizando NaOH (24 gramos). La pasta acuosa resultante se extrajo con dietil-éter (300 mililitros, 6 veces), se secó utilizando sulfato de sodio, y se removió el dietil-éter utilizando un evaporador giratorio para proporcionar la cloro-imidazo-[1,2-b]-piridazina (10-1) como un sólido color naranja claro. MS: 155.1 $[M+1]^+$.

Esquema 11



10-1 11-1

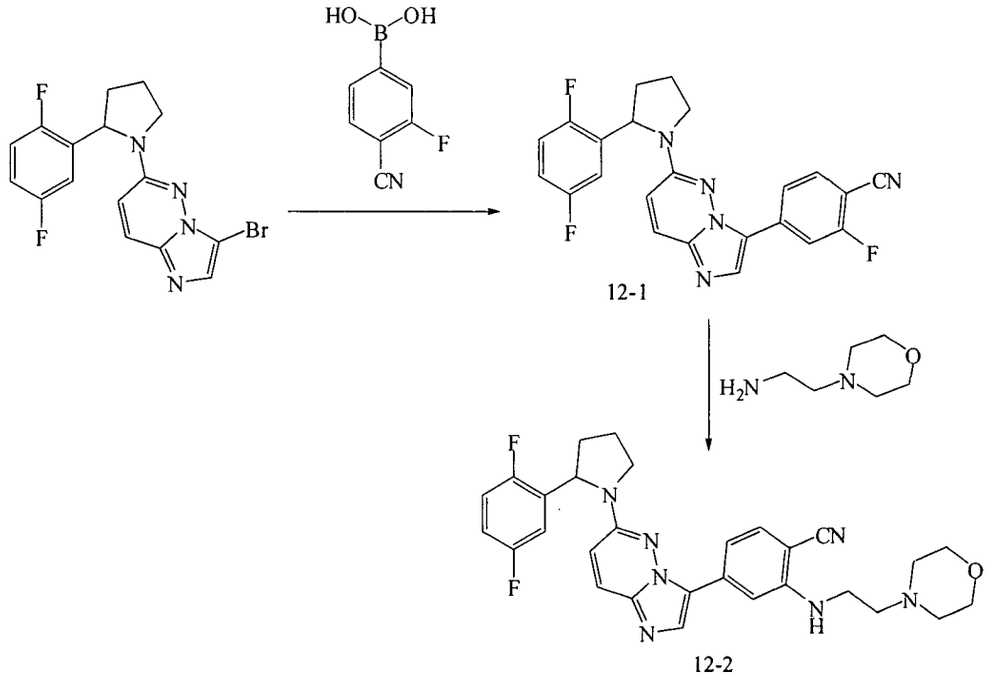
Ejemplo 11

3-bromo-6-cloro-imidazo-[1,2-b]-piridazina

La 3-bromo-6-cloro-imidazo-[1,2-b]-piridazina (11-1) se sintetizó como se muestra en el esquema 11, en donde se agregó N-

bromo-succinamida (19.2 gramos, 108 milimoles) a una solución de cloro-imidazo-[1,2-b]-piridazina (10-1) (15 gramos, 98 milimoles) en N,N-dimetil-formamida enfriada a 0°C. La solución resultante se agitó a 0°C durante 1 hora, y la mezcla de reacción se vertió entonces en 1.4 litros de agua en agitación a temperatura ambiente. La solución heterogénea amarilla resultante se agitó entonces a temperatura ambiente durante una hora, y los sólidos entonces se filtraron y se lavaron con hexanos. El sólido se secó al vacío durante la noche para proporcionar la 3-bromo-6-cloro-imidazo-[1,2-b]-piridazina (11-1) como un sólido amarillo.

Esquema 12



12-2

Ejemplo 12

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-morfolino-etil-amino)-benzonitrilo

El 14-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-morfolino-etil-amino)-benzonitrilo (12-2) se sintetizó en dos pasos como se muestra en el esquema 12.

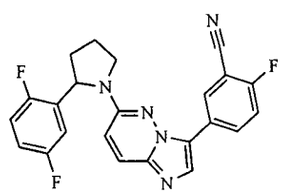
En el paso 12-1, se agregaron $[Pd(Dppf)_2]Cl_2$ (90 miligramos, 0.11 milimoles), carbonato de sodio (0.41 gramos, 3.9 milimoles), y ácido 4-ciano-3-fluoro-fenil-borónico (0.36 gramos, 2.2 milimoles) a una solución de 3-bromo-6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina (6-6) (0.42 gramos, 1.1 milimoles) en 3 mililitros de dioxano y 1 mililitro de agua desionizada. La mezcla de reacción se calentó en un reactor de microondas durante veinte minutos a 150°C, y la pasta acuosa se enfrió entonces a temperatura ambiente, y se filtró a través de una frita de nylon de 0.2 micras. El solvente se removió a partir del licor madre, y el residuo restante se reconstituyó en dicloro-metano (DCM). Esta solución se cargó en una columna de 12 gramos de gel de sílice, y se eluyó utilizando un gradiente del 0 al 10 por ciento de metanol en dicloro-metano durante 30 minutos. El solvente se removió a partir de las fracciones deseadas para proporcionar el 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-fluoro-benzonitrilo. m/z = 420.2 [M+1].

En el paso 12-2, se agregó 2-morfolino-etanamina (30 miligramos, 0.30 milimoles) al 4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-fluoro-benzonitrilo (40 miligramos, 0.13 milimoles) en 1 mililitro de N,N-dimetil-formamida. La mezcla resultante se calentó a 110°C, y se agitó durante 12 horas a 110°C.

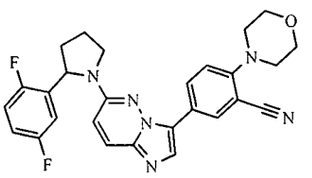
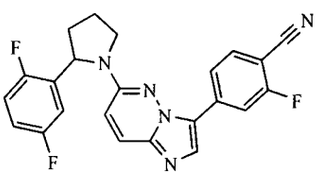
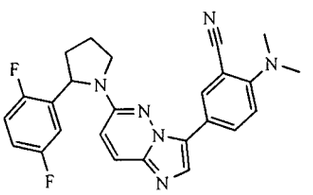
El producto se purificó entonces utilizando LC/MS de preparación desencadenada por la masa, dando el 1-(6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol (13-2). ^{1}H RMN (400 MHz, D_6 sulfóxido de dimetilo) 8.050 (s, 1H) 7.854 (d, 0.025, 1H) 7.434 (br s, 1H) 7.327 (dt, J = 0.023, 0.011, 1H) 7.262 (m, 1H) 7.173 (m, 1H) 7.070 (m, 1H) 6.937 (m, 1H) 6.747 (br s, 1H) 5.770 (t, J = 0.012, 1H) 5.244 (d, J = 0.019, 1H) 3.949 (dt, J = 0.017, 0.006, 1H) 3.575 (q, J = 0.023, 1H) 3.522 (t, J = 0.011, 4H) 3.268 (m, 4H) 2.536 (t, J = 0.016, 2H) 1.985 (m, 3H) LCMS *m/z* 530.2 [M+1]

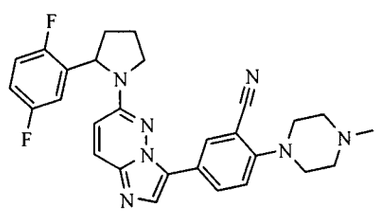
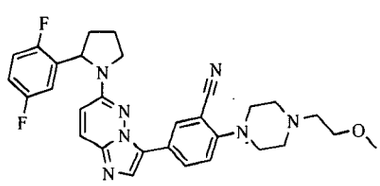
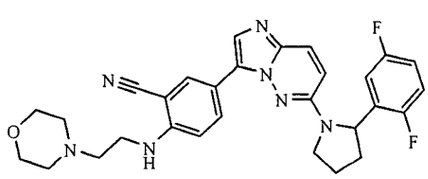
Mediante la repetición de los procedimientos descritos en los ejemplos anteriores, utilizando los materiales de partida apropiados, se obtuvieron los siguientes compuestos de la fórmula (I), como se identifican en la Tabla 5.

Tabla 5

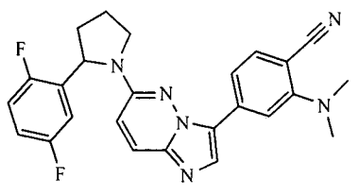
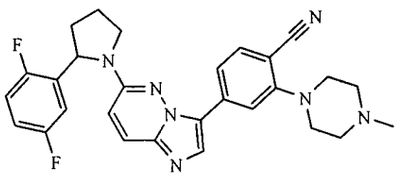
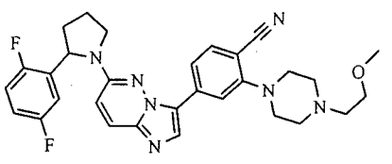
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
1		420.4 (M+H)

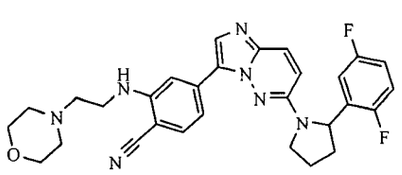
310

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
2		487.5 (M+H)
3		487.5 (M+H)
4		8.247 (s, 1H) 8.192 (br s, 1H) 8.071 (d, J = 0.024, 1H) 7.926 (br s, 1H) 7.341 (dt, J= 0.024, 0.011, 1H) 7.139 (m, 2H) 7.037 (m, 1H) 6.929 (m, 1H) 5.332 (d, J = 0.018, 1H) 4.033 (m, 1H) 3.652 (q, J = 0.023, 2H) 3.090 (s, 6H) 2.122 (m, 3H) 445.5 (M+H)

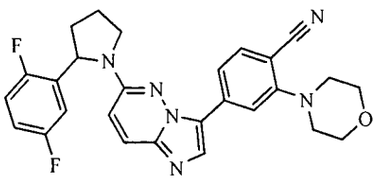
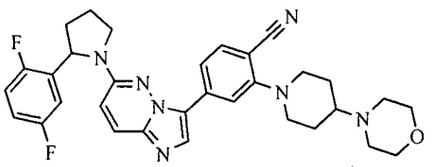
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
5		8.212 (br s, 1H) 8.019 (br s, 1H) 7.927 (s, 1H) 7.849 (d, J = 0.024, 1H) 7.274 (dt, J= 0.024, 0.012, 1H)7.046 (m, 1H) 6.950 (m, 2H) 6.782 (m, 1H) 5.250 (d, J = 0.019, 1H) 3.933 (dt, J = 0.024, 0.006, 1H) 3.553 (q, 0.022, 1H) 3.132 (t, J= 0.012, 3H) 2.473 (m, 6H) 2.197 (s, 3H) 1.986 (m, 3H) 500.6 (M+H)
6		544.6 (M+H)
7		530.6 (M+H)

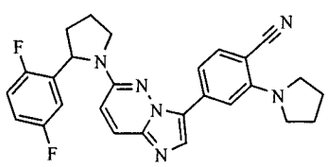
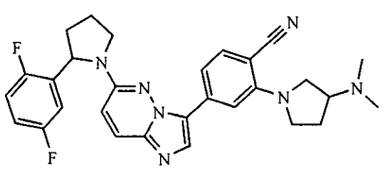
311

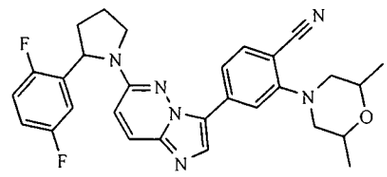
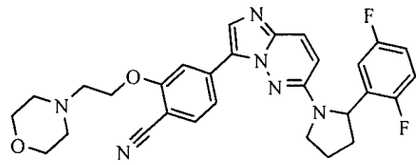
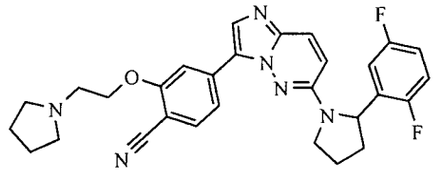
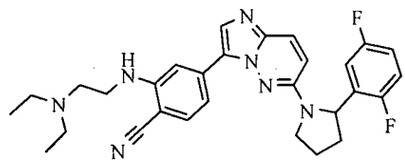
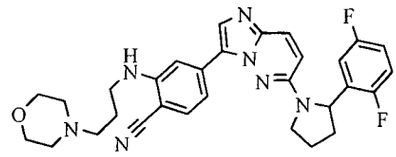
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
8		445.5 (M+H)
9		9.935 (br s, 1H) 8.364 (s, 1H) 8.019 (d, J = 0.024, 1H) 7.626 (m, 2H) 7.430 (dt, J = 0.024, 0.011, 1H) 7.153 (m, 1H) 7.033 (m, 2H) 5.325 (d, J = 0.019, 1H) 4.035 (dt, J = 0.019, 0.006, 1H) 3.727 (d, J = 0.028, 2H) 3.603 (m, 3H) 3.241 (m, 4H) 2.926 (s, 3H) 2.090 (m, 4H) 500.6 (M+H)
10		9.840 (br s, 1H) 8.335 (s, 1H) 8.007 (d, J = 0.025, 1H) 7.622 (m, 2H) 7.429 (m, 1H) 7.153 (m, 1H)

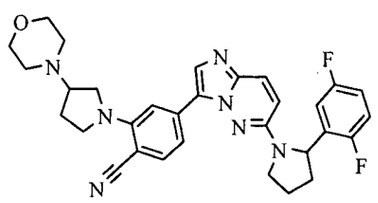
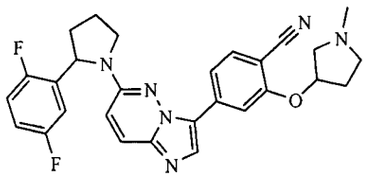
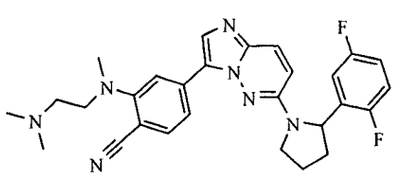
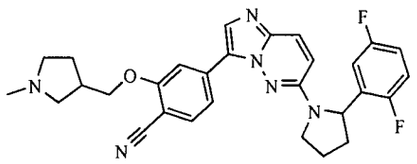
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		7.033 (m, 2H)5.324 (d, J = 0.019, 1H) 4.035 (dt, J =0.019, 0.007, 1H) 3.724 (m, 9H) 3.357 (s, 3H) 3.305 (m, 4H) 2.122 (m, 4H) 544.6 (M+H)
11		8.050 (s, 1H) 7.854 (d, 0.025, 1H) 7.434 (br s, 1H) 7.327 (dt, J = 0.023, 0.011, 1H) 7.262 (m, 1H) 7.173 (m, 1H) 7.070 (m, 1H) 6.937 (m, 1H) 6.747 (br s, 1H) 5.770 (t, J = 0.012, 1H) 5.244 (d, J = 0.019, 1H) 3.949 (dt, J = 0.017, 0.006, 1H) 3.575 (q, J = 0.023, 1H) 3.522 (t, J = 0.011, 4H) 3.268 (m, 4H) 2.536 (t, J =

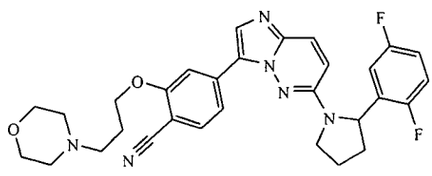
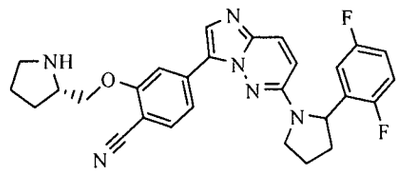
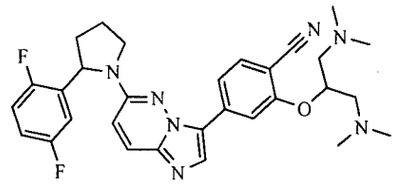
312

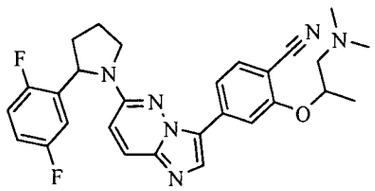
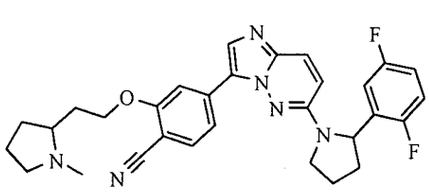
# Comp.	Estructura	Datos Físicos ¹H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		0.016, 2H) 1.985 (m, 3H) 530.6 (M+H)
12		487.5 (M+H)
13		9.908 (br s, 1H) 8.362 (s, 1H) 8.046 (d, J = 0.025, 1H) 7.600 (br s, 2H) 7.437 (dt, J =0.024, 0.011, 1H) 7.155 (m, 1H) 7.032 (m, 2H) 5.330 (d, J = 0.019, 1H) 4.035 (d, J = 0.024, 3H) 3.698 (m, 5H) 3.543 (d, J = 0.030, 2H) 3.409 (m, 2H) 3.182 (m, 2H) 2.898 (t, J = 0.030, 2H) 2.277(d, J = 0.026, 2H) 1.950 (m, 5H)

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		570.6 (M+H)
14		8.230 (s, 1H) 7.910 (d, J = 0.025, 1H) 7.239 (m, 2H) 7.008 (m, 3H) 6.867 (m, 2H) 5.178 (d, J = 0.020, 1H) 3.883 (t, J = 0.019, 2H) 3.441 (m, 5H) 1.829 (m, 7H) 471.5 (M+H)
15		9.934 (br s, 1H) 8.264 (s, 1H) 7.994 (d, J = 0.025, 1H) 7.419 (m, 3H) 7.154 (m, 1H) 7.024 (m, 2H) 5.310 (m, 1H) 3.799 (m, 12H) 2.904 (d, J = 0.019, 4H) 2.228 (m, 1H) 2.0677(m, 2H) 514.6 (M+H)

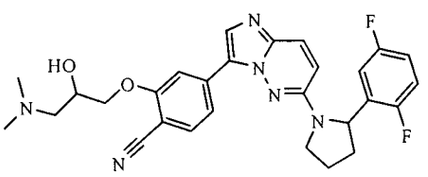
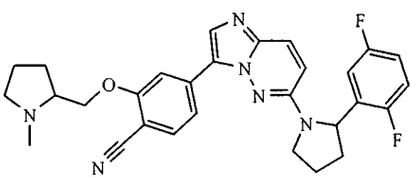
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
16		515.6 (M+H)
17		531.6 (M+H)
18		515.6 (M+H)
19		515.6 (M+H)
20		9.747 (br s, 1H) 8.280 (d, J = 0.009, 1H) 7.999 (m, 1H) 7.419 (m, 3H) 7.132 (m, 3H) 6.297 (br s, 1H) 5.313 (d, J = 0.019, 1H) 4.001 (m, 4H) 3.625 (m, 3H) 3.433 (m, 4H) 3.197

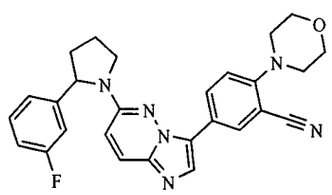
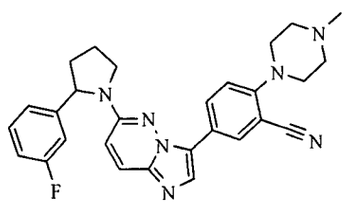
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(m, 4H) 1.994 (m, 5H) 544.6 (M+H)
21		556.6 (M+H)
22		501.5 (M+H)
23		502.6 (M+H)
24		515.6 (M+H)

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
25		545.6 (M+H)
26		9..321 (m, 1H) 8.935 (m, 1H) 8.365 (m,1H) 7.998 (m, 1H) 7.743 (m, 2H) 7.408 (m, 1H) 7.147 (m, 1H) 7.034 (m,1H) 5.321 (d, J = 0.019, 1H) 4.530 (m, 2H) 4.371 (m, 2H) 4.048 (m, 2H) 3.674 (m, 1H) 3.281 (m, 2H) 2.216 (m,1H) 2.072 (m, 3H) 1.947 (m, 3H) 501.5 (M+H)
27		546.6 (M+H)

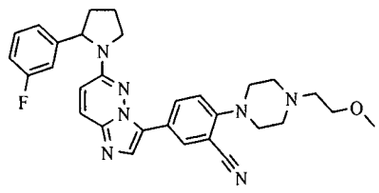
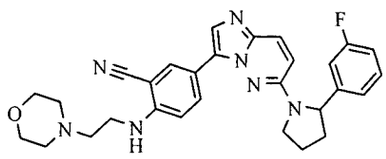
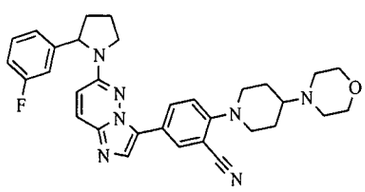
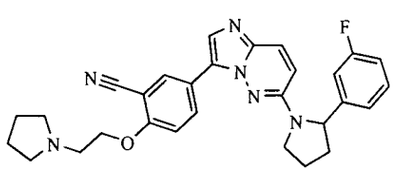
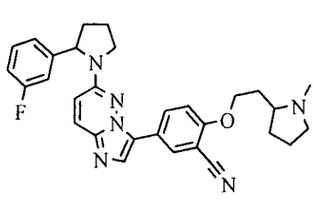
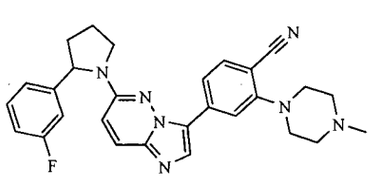
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
28		9.774 (br s, 1H) 8.374 (s, 1H) 8.014 (m, 1H) 7.863 (m, 1H) 7.726 (m, 1H) 7.632 (m, 1H)7.453 (m, 1H) 7.152 (m, 1H) 7.047 (m, 1H) 5.327 (m, 2H) 5.203 (d, J = 0.02, 1H) 4.533 (m, 1H) 4.038 (m, 1H) 3.653 (m, 1H) 3.543 (m, 2H) 2.920 (m, 4H) 2.046 (m, 2H) 1.914 (m, 1H) 1.349 (d, J = 0.015, 2H) 503.6 (M+H)
29		9.584 (br s, 1H) 8.324 (s, 1H) 7.988 (m, 1H) 7.697 (m, 1H) 7.608 (m, 1H) 7.428 (m, 2H) 7.145 (m,

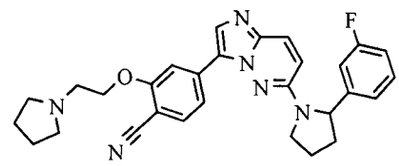
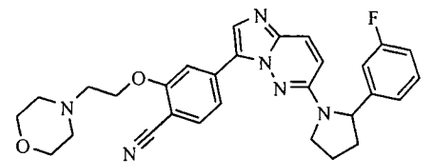
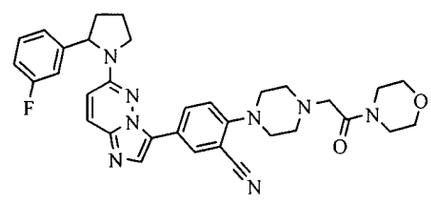
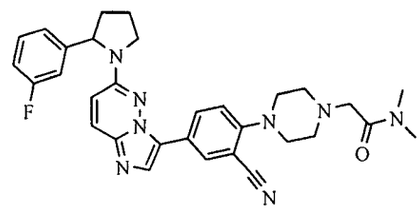
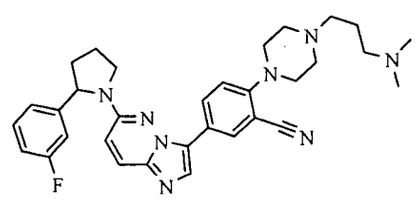
315

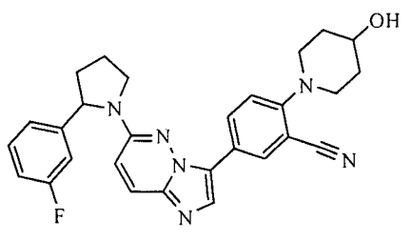
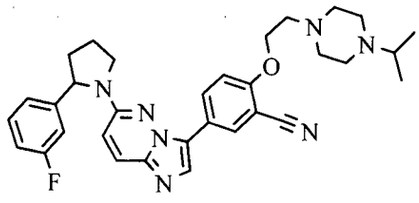
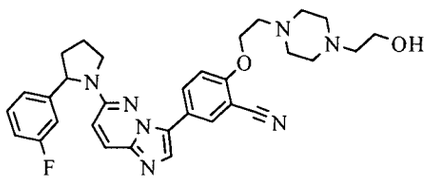
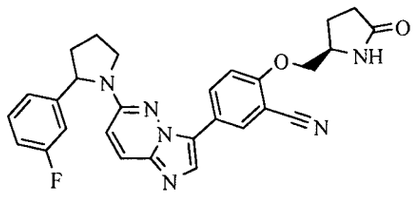
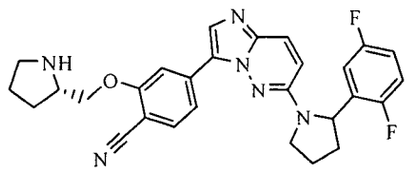
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1H) 7.033 (m, 1H) 5.337 (d, J = 0.019, 1H) 4.342 (m, 3H) 4.041 (m, 2H) 3.644 (m,3H) 3.415 (m, 1H) 3.132 (m, 1H) 2.922 (d, J = 0.013, 2H) 2.334 (m, 1H) 2.036 (m, 6H) 1.829 (m, 1H) 529.6 (M+H)
30		519.6 (M+H)
31		9.973 (br s, 1H) 8.358 (m, 1H) 7.994 (m, 2H) 7.764 (m, 1H), 7.667 (m, 1H) 7.410 (m, 1H) 7.147 (m, 1H) 7.034 (m, 2H) 5.343 (d, J=0.02, 1H) 4.655 (m, 2H) 4.390 (m, 2H) 4.038 (m, 2H)3.657 (m, 2H)

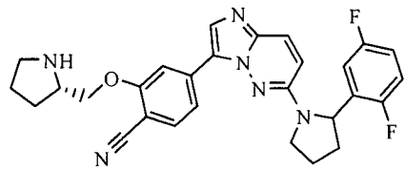
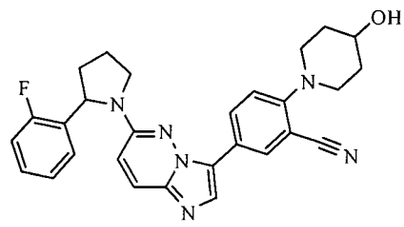
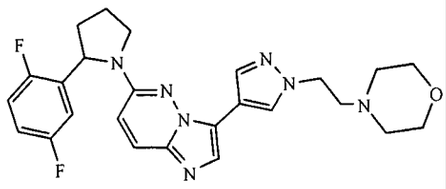
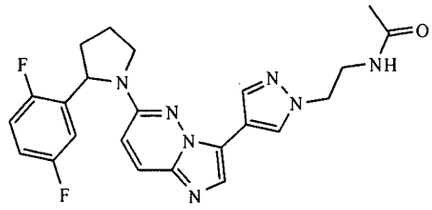
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		3.191 (m, 1H) 2.334 (m, 1H) 2.122 (m, 5H) 515.6 (M+H)
32		8.367 (br d, 1H) 8.221 (d, J = 0.013, 1H) 7.952 (t, J = 0.024, 1H) 7.142 (m, 7H) 5.151 (dd, J = 0.016, 0.004, 1H) 3.930 (m, 2H) 3.738 (t, J = 0.011, 4H) 3.614 (t, J = 0.021, 2H) 3.174 (m, 3H) 1.977 (m, 2H) 1.826 (m, 1H) 469.5 (M+H)
33		482.6 (M+H)

316

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
34		526.6 (M+H)
35		512.6 (M+H)
36		552.7 (M+H)
37		497.6 (M+H)
38		511.6 (M+H)
39		482.6 (M+H)

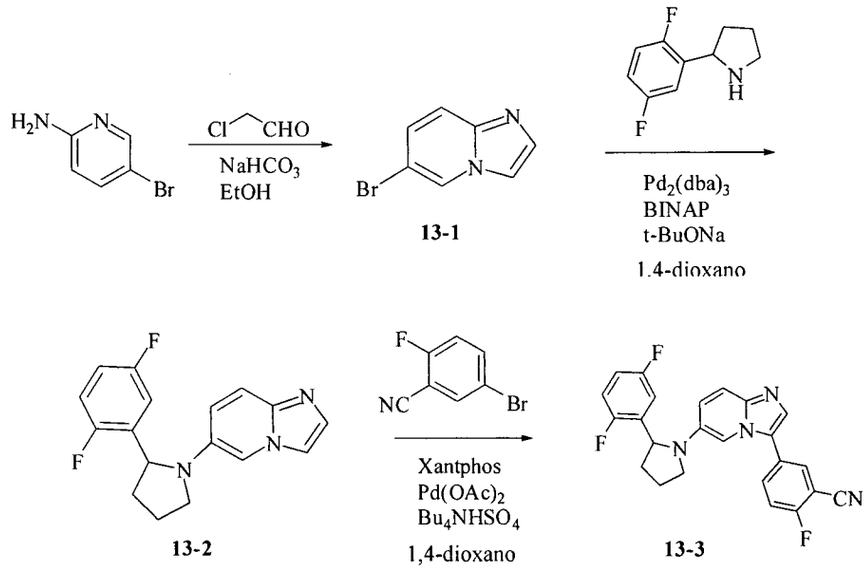
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
40		497.6 (M+H)
41		513.6 (M+H)
42		595.7 (M+H)
43		553.6 (M+H)
44		553.7 (M+H)

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
45		483.6 (M+H)
46		554.7 (M+H)
47		556.6 (M+H)
48		497.5 (M+H)
49		501.5 (M+H)

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
50		501.5 (M+H)
51		483.6 (M+H)
52		480.5 (M+H)
53		452.5 (M+H)

318

Esquema 13



Ejemplo 13

5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-a]-piridin-3-il)-2-fluoro-benzonitrilo

El 5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-a]-piridin-3-il)-2-fluoro-benzonitrilo (13-3) se sintetizó en tres pasos como se muestra en el esquema 13.

En el paso 13-1, se agregaron cloro-acetaldehído (al 55 por ciento en agua, 0.27 mililitros, 4.5 milimoles), y $NaHCO_3$ (143 miligramos, 1.7 milimoles) a una solución de 5-bromo-piridin-2-amina (173 miligramos, 1 milimol) en EtOH (7 mililitros). La mezcla se calentó a reflujo y se continuó durante la noche. La mezcla de reacción se enfrió a temperatura ambiente, y se concentró al vacío. Se agregó dicloro-metano, se extrajo el residuo. La capa orgánica se lavó con agua, salmuera, se secó sobre Na_2SO_4, se filtró, y se

evaporó, para dar el producto crudo. El producto crudo se purificó mediante cromatografía en columna (gradiente de gel de sílice, EtOAc/Hexano), para dar la 6-bromo-imidazo-[1,2-a]-piridina (13-1).

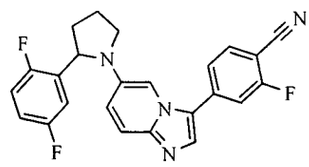
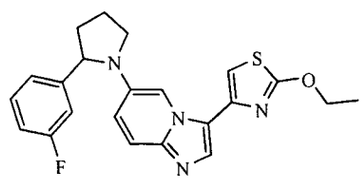
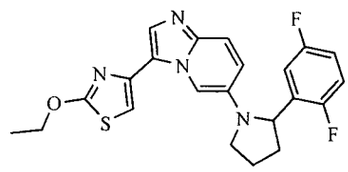
En el paso 13-2, un frasco para microondas se cargó con 6-bromo-imidazo-[1,2-a]-piridina (197 miligramos, 1 milimol), 2-(2,5-difluoro-fenil)-pirrolidina (238 miligramos, 1.3 milimoles), $Pd_2(dba)_3$ (18 miligramos, 0.02 milimoles), BINAP (50 miligramos, 0.08 milimoles), t-BuONa (135 miligramos, 1.4 milimoles), y 1,4-dioxano (5 mililitros), y la mezcla se calentó a 120°C durante 30 minutos utilizando irradiación de microondas. La mezcla se filtró a través de Celite. El filtrado se concentró y se purificó mediante cromatografía en columna (gradiente de gel de sílice, EtOAc/hexano), para dar la 6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-a]-piridina (13-2).

En el paso 13-3, un frasco sellado se cargó con 6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-a]-piridina (30 miligramos, 0.1 milimoles), 5-bromo-2-fluoro-benzonitrilo (20 miligramos, 0.1 milimoles), $Pd(OAc)_2$ (1 miligramos, 0.005 milimoles), Xantphos (6 miligramos, 0.01 milimoles), Cs_2CO_3 (49 miligramos, 0.15 milimoles), Bu_4NHSO_4 (3 miligramos, 0.01 milimoles), y 1,4-dioxano (0.5 mililitros), y la mezcla se calentó a 90°C durante la noche. La mezcla se filtró a través de Celite. El filtrado se concentró y se purificó mediante LC-MS de preparación, para dar el 5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-a]-piridin-3-il)-2-fluoro-benzonitrilo (12-3). LC-MS: 419.2 (MH^+).

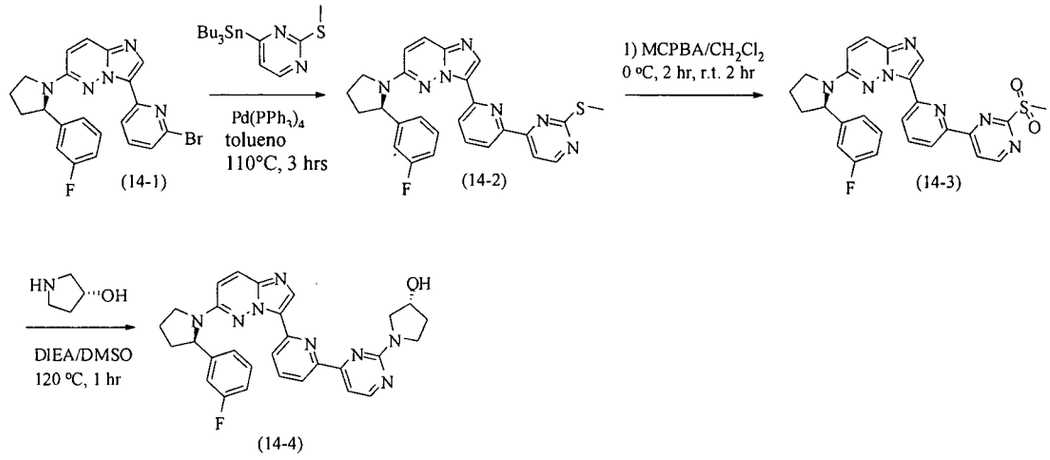
Mediante la repetición de los procedimientos descritos en el

Ejemplo 13, utilizando los materiales de partida apropiados, se obtuvieron los siguientes los compuestos de la fórmula I, como se identifican en la Tabla 6.

Tabla 6

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
1		419.1 (M+H)
2		427.2 (M+H)
3		409.2 (M+H)

Esquema 14



Ejemplo 14

El (R)-1-(4-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-pirrolidin-3-ol (14-4) se sintetizó en tres pasos como se muestra en el esquema 14.

En el paso 14-1, se agregaron 2-(tiometil)-4-(tributil-estanil)-pirimidina (4.3 gramos, 13.2 milimoles), y $Pd(PPh_3)_4$ (196 miligramos, 0.17 milimoles) a una solución de (R)-3-(6-bromo-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina (14-1) (1.5 gramos, 3.4 milimoles) en tolueno (35 mililitros). La mezcla se desgasificó utilizando N_2 durante 15 minutos, y entonces se calentó a 110°C durante 2 horas. Todos los solventes se removieron. La mezcla resultante se purificó mediante cromatografía en columna (gel de sílice, EtOAc/CH_3OH, gradiente de del 0 al 10 por ciento), para dar la (R)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(2-(tiometil)-pirimidin-4-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina (14-2) como una espuma color amarillo claro. LC/MS: 484.2 (MH+).

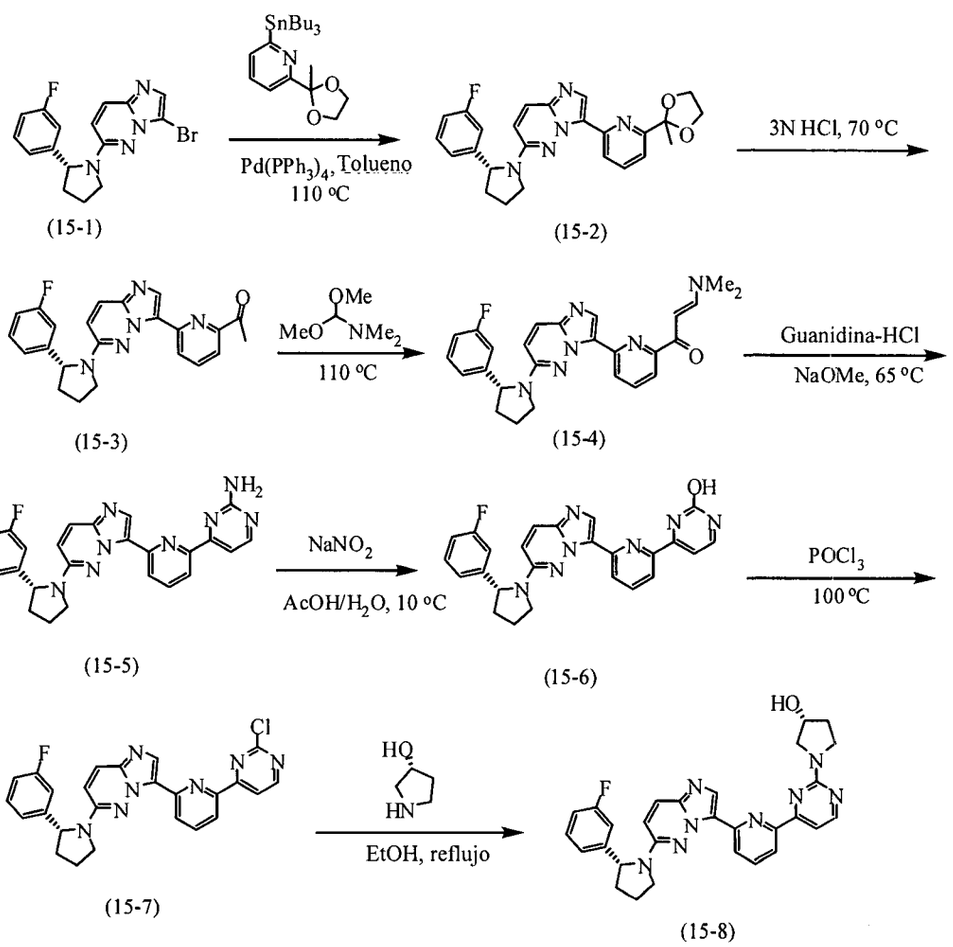
320

En el paso 14-2, una solución de MCPBA (720 miligramos, 3.2 milimoles) en CH_2Cl_2 (15 mililitros), se agregó lentamente a una solución de (R)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(2-(tiometil)-pirimidin-4-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina (14-2) (776 miligramos, 1.6 milimoles) en CH_2Cl_2 (16 mililitros) a 0°C. La mezcla se agitó a 0°C durante 1 hora, y entonces se calentó a temperatura ambiente. La mezcla se agitó luego a temperatura ambiente durante 2 horas. La mezcla se diluyó con CH_2Cl_2 (100 mililitros), y se lavó con NaOH 1N (75 mililitros, 2 veces), y salmuera (75 mililitros, 2 veces). La capa orgánica se separó, se secó sobre Na_2SO_4 y se concentró. La mezcla se purificó mediante cromatografía en columna (gel de sílice, CH_2Cl_2/CH_3OH, gradiente de 2 a 5 por ciento). La (R)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(2-(metil-sulfonil)-pirimidin-4-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina (14-3) se obtuvo como un sólido amarillo claro. LC/MS: 516.2 (MH+). También se obtuvo la 6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(2-(metil-sulfinil)-pirimidin-4-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina.

En el paso 14-3, se agregaron (R)-pirrolidin-3-ol (136 miligramos, 1.56 milimoles), y DIEA (453 microlitros, 2.6 milimoles) a una solución de (R)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(2-(metil-sulfonil)-pirimidin-4-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina (14-3) (268 miligramos, 0.52 milimoles) en sulfóxido de dimetilo (3 mililitros). La mezcla se calentó a 120°C durante 1 hora. La mezcla se diluyó con CH_2Cl_2, se lavó con H_2O y salmuera, se secó sobre Na_2SO_4, se filtró, y se concentró. La mezcla se purificó mediante

cromatografía en columna (gel de sílice, CH_2Cl_2/CH_3OH, gradiente del 5 por ciento), para dar el (R)-1-(4-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-pirrolidin-3-ol (14-4). LC/MS: 523.2 (MH+).

Esquema 15



Ejemplo 15

El (R)-1-(4-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-pirrolidin-3-ol también

se sintetizó en siete pasos como se muestra en el esquema 15.

En el paso 15-1, la 2-(2-metil-1,3-dioxolan-2-il)-6-(tributil-estanil)-piridina (57 gramos, 124 milimoles) en 100 mililitros de tolueno se transfirió por medio de una cánula, bajo una atmósfera argón, a una suspensión de 3-bromo-6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina (15-1) (30 gramos, 83 milimoles), y tetraquis-(trifenil-fosfina)-paladio (4.8 miligramos, 4.15 milimoles) en 500 mililitros de tolueno. La mezcla de reacción resultante se calentó a 110°C durante la noche. El progreso de la reacción se monitoreó mediante LC/Masa. Después de que la reacción estuvo completa, el recipiente de reacción se enfrió a temperatura ambiente y el solvente se redujo a 1/3 del volumen original. La purificación se llevó a cabo mediante cromatografía por evaporación instantánea utilizando acetato de etilo puro, para proporcionar la (*R*)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(2-metil-1,3-dioxolan-2-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina (15-2). ^{1}H RMN (400 MHz, DMSO-d6) δ 8.10 (s, 1H), 8.09 (s br, 1H), 7.93 (d, 1H, J = 9.6 Hz), 7.72 (m, 1H), 7.39 (m, 2H), 7.18 (m, 2H), 7.04 (m, 1H), 6.89 (br s, 1H), 5.16 (d, 1H, J = 8.0 Hz), 4.02 (m, 3H), 3.91 (m, 2H), 3.68 (m, 2H), 2.48 (m, 1H), 2.05 (m, 2H), 1.88 (m, 1H), 1.69 (s, 3H). LCMS: *m/z* 446.2 (M+1).

En el paso 15-2, la (*R*)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(2-metil-1,3-dioxolan-2-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina (15-2) (30 gramos, 67.4 milimoles) se cargó con una mezcla de tetrahidrofurano (150 mililitros) y HCl 2N (450 mililitros), y la

solución resultante se calentó a 70°C durante la noche. Se utilizó LC/MS para confirmar que la reacción estaba completa. La mezcla de reacción entonces se neutralizó utilizando NaOH 10N, dando como resultado la formación de la (*R*)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazol[1,2-b]-piridazin-3-il)-piridin-2-il)-etanona (15-3) como un precipitado amarillo pálido, el cual se filtró y se secó (Nota: el producto necesita estar seco para el paso 15-3 debido a que cualquier cantidad de agua hace que la reacción sea fangosa). ^{1}H RMN: ppm 8.52 (s, 1H), 8.32 (br s, 1H), 8.10 (d, 1H, J = 10 Hz), 7.96 (br s, 1H), 7.87 (d, 1H, J = 7.6 Hz), 7.41 (m, 1H), 7.20 (m, 3H), 7.05 (m, 1H), 5.23 (dd, 1H, J = 8.2 Hz, 2 Hz), 4.06 (m, 1H), 3.72 (q, 1H, J = 8.0 Hz), 2.71 (s, 3H), 2.51 (m, 1H), 2.07 (m, 2H), 1.91 (m, 1H). LCMS: *m/z* 446.2 (M+1).

En el paso 15-3, una mezcla de (*R*)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazol[1,2-b]-piridazin-3-il)-piridin-2-il)-etanona (15-3) (25 gramos, 62.3 milimoles), y dimetil-acetal de dimetil-formamida (300 mililitros) se calentó durante la noche a reflujo, y entonces se enfrió a temperatura ambiente. Los volátiles se removieron mediante evaporación giratoria bajo presión reducida, y los residuos sólidos se trituraron con 200 mililitros de una mezcla de EtOAc/Hexano (1:5), y se filtraron, para dar la (*R,E*)-3-(dimetil-amino)1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazol[1,2-b]-piridazin-3-il)-piridin-2-il)-prop-2-en-1-ona (15-4) como un sólido amarillo, el cual se utilizó en el siguiente paso sin mayor purificación.

En el paso 15-4, el metóxido de sodio preparado recientemente

en metanol (400 mililitros) se transfirió por medio de una cánula a una solución de (*R,E*)-3-(dimetil-amino)1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazol[1,2-b]-piridazin-3-il)-piridin-2-il)-prop-2-en-1-ona (15-4) y guanidina-HCl en metanol (200 mililitros). La suspensión resultante se calentó durante la noche a 65°C. El progreso de la reacción se monitoreó mediante LC/Masa. Después de que la reacción estuvo completa, la mezcla de reacción se neutralizó con HCl acuoso 4N, y entonces se agitó durante 1 hora a temperatura ambiente. La mezcla de reacción se filtró, para dar la (R)-4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-amina (15-5) como un sólido amarillo. ^{1}H RMN: ppm 8.42 (d, 1H, J = 4.8 Hz), 8.31 (s, 1H), 8.16 (d, 1H, J = 8.0 Hz), 7.96 (d, 1H, J = 10 Hz), 7.89 (m, 1H), 7.64 (d, 1H, J = 4.8 Hz), 7.42 (ddd, 1H, J = 8.0, 8.0, 6.0 Hz), 7.20 (m, 2H), 7.05 (ddd, 1H, J = 8.4, 8.4, 2.0 Hz), 6.91 (br s, 1H), 6.76 (s, 2H), 5.22 (dd, 1H, J = 8.2 Hz, 2.4 Hz), 4.03 (m, 1H), 3.70 (q, 1H, J = 8.4 Hz), 2.51 (s, 1H), 2.06 (m, 2H), 1.90 (m, 1H), 1.18 (d, 1H, J = 6.4Hz). LCMS: *m/z* 453.2 (M+1).

En el paso 15-5, una solución acuosa de nitrito de sodio ($NaNO_2$) se agregó por goteo a una solución de (R)-4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-amina (15-5) (20 gramos, 44.2 milimoles) en AcOH (250 mililitros) y H_2O (250 mililitros), mientras que se mantenía la temperatura entre 5°C y 10°C. El progreso de la reacción se monitoreó mediante LC/MS. Después de que la reacción estuvo completa, los solventes se concentraron a sequedad, y el residuo

entonces se trató con K_2CO_3 en metanol. La mezcla resultante entonces se neutralizó con HCl 3N, el solvente se concentró, y la mezcla entonces se extrajo con dicloro-metano (3 veces). El extracto se secó sobre Na_2SO_4, se filtró, y se concentró bajo presión reducida, para dar el producto crudo, el cual se purificó mediante cromatografía en columna (10 por ciento de metanol en CH_2Cl_2 con incremento en la cantidad de metanol hasta el 15 por ciento), para proporcionar el (*R*)-4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazol-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-ol (15-6) como un sólido amarillo. ^{1}H RMN: ppm 12.1 (s, 1H), 8.32 (s, 1H), 8.16 (d, 1H, J = 8.0 Hz), 7.95 (d, 1H, J = 10 Hz), 7.90 (m, 1H), 7.49 (d, 1H, J = 6.4 Hz), 7.42 (ddd, 1H, J = 8.0, 8.0, 6.4 Hz), 7.20 (m, 2H), 7.05 (ddd, 1H, J = 8.4, 8.4, 2.4 Hz), 6.91 (br s, 1H), 5.2 (dd, 1H, J = 8.2 Hz, 2.4 Hz), 4.02 (m, 1H), 3.69 (q, 1H, J = 8.0 Hz), 2.49 (m, 2H), 2.05 (m, 2H), 1.89 (m, 1H). LCMS: 454.2 (M+1).

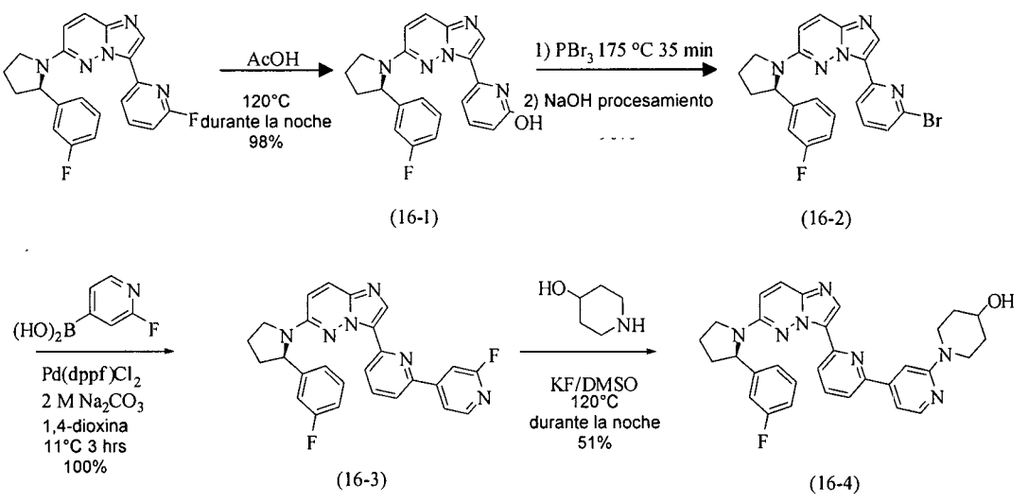
En el paso 15-6, el (*R*)-4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazol[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-ol (15-6) (15 gramos, 33.2 milimoles) se cargó con $POCl_3$ (200 mililitros), y entonces se calentó durante la noche a 100°C. El progreso de la reacción se monitoreó mediante LC/MS. Después de que la reacción estuvo completa, los residuos volátiles se removieron mediante destilación bajo presión reducida. Después de la remoción de la mayoría de los $POCl_3$, los sólidos resultantes se disolvieron con dicloro-metano y se neutralizaron con K_2CO_3 acuoso. Los solventes orgánicos se secaron sobre Na_2SO_4, se filtraron, y se concentraron

con un evaporador giratorio bajo presión reducida, para dar un sólido amarillo crudo, el cual se purificó mediante cromatografía en columna (5 por ciento de metanol en CH_2Cl_2), para dar la (*R*)-3-(6-(2-cloro-pirimidin-4-il)-pirimidin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazol[1,2-b]-piridazina (15-7) como un sólido amarillo. ^{1}H RMN: ppm 8.93 (d, 1H, J = 4.8 Hz), 8.58 (d, 1H, J = 2.8 Hz), 8.41 (s, 1H), 8.34 (br s, 1H), 8.22 (d, 1H, J = 8.0 Hz), 7.95 (m, 2H), 7.41 (ddd, 1H, J = 8.0, 8.0, 6.4 Hz), 7.20 (m, 2H), 7.05 (ddd, 1H, J = 8.4, 8.4, 2.4 Hz), 6.92 (br s, 1H), 5.21 (dd, 1H, J = 8.2 Hz, 2.4 Hz), 4.03 (m, 1H), 3.70 (q, 1H, J = 8.0 Hz), 2.47 (m, 2H), 2.06 (m, 2H), 1.90 (m, 1H). LCMS: 472.2 (M+1).

En el paso 15-7, se agregó (R)-3-hidroxilo pirrolidina a una solución de la (*R*)-3-(6-(2-cloro-pirimidin-4-il)-pirimidin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazol-[1,2-b]-piridazina (15-7) (10 gramos, 21.2 milimoles) en etanol (100 mililitros), y la mezcla resultante se calentó a reflujo durante 7 horas. Los residuos volátiles se removieron por medio de un evaporador giratorio bajo presión reducida, seguido por cromatografía en columna, para dar el (R)-1-(4-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-pirrolidin-3-ol como un sólido amarillo pálido. ^{1}H RMN: ppm 8.51 (d, 1H, J = 5.2 Hz), 8.32 (s, 1H), 8.30 (br s, 1H), 8.24 (d, 1H, J = 7.6 Hz), 7.93 (d, 1H, J = 10 Hz), 7.86 (m, 1H), 7.65 (d, 1H, J = 4.8 Hz), 7.40 (ddd, 1H, J = 8.0, 8.0, 6.4 Hz), 7.20 (s, 1H), 7.17 (m, 1H), 7.04 (ddd, 1H, J = 8.4, 8.4, 2.4 Hz), 6.85 (br s, 1H), 5.17 (dd, 1H, J = 8.2 Hz, 2.4 Hz), 5.01 (d, 1H, J = 3.2 Hz),

4.43 (br s, 1H), 4.02 (m, 1H), 3.65 (m, 5H), 2.45 (m, 1H), 2.05 (m, 3H), 1.89 (m, 2H). 13C NMR: ppm 163.58, 162.17, 161.16, 160.15, 159.14, 153.65, 151.80, 147.53, 147.13(d, J =25.6 Hz), 137.66, 133.20, 130.39(d, J = 30.4 Hz), 126.44, 126.06, 121.64, 120.67, 118.52, 113.45 (d, J = 83.2 Hz), 112.40 (d, J = 87.6 Hz), 110.31, 104.90, 69.10, 61.26, 54.82, 48.39, 44.42, 35.27, 33.47, 22.66. LCMS: 523.2 (M+1).

Esquema 16



Ejemplo 16

El (R)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-piperidin-4-ol (16-4) se sintetizó en cuatro pasos como se muestra en el esquema 16.

En el paso 16-1, una suspensión de (R)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-fluoro-piridin-2-il)-imidazo-[1,2-b]-piridazina (16 gramos, 42 milimoles) en ácido acético (150 mililitros) se calentó durante la noche a 120°C (aproximadamente 20 horas). La

suspensión se volvió transparente después de calentar. La mezcla se concentró al vacío, para dar un aceite color café. El aceite se disolvió en CH_2Cl_2 (750 mililitros), y se lavó con $NaHCO_3$ saturado (300 mililitros, 3 veces), y salmuera (300mililitros, 2 veces). La capa orgánica se separó, se secó sobre (Na_2SO_4), y se concentró para dar 15.5 gramos del (R)-6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-ol (16-1) crudo, el cual se utilizó en el siguiente paso sin mayor purificación. LC/MS: 376.2 ($M+H^+$).

En el paso 16-2, una suspensión de (R)-6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-ol (16-1) crudo (13.3 gramos, 35.4 milimoles) en PBr_3 (25 mililitros) se calentó a 175°C durante 35 minutos. Mientras la mezcla se calentaba, se vertió en NaOH 2N (1.2 litros) helado. El sólido se recolectó mediante filtración y se lavó con H_2O. El producto final se secó bajo un alto vacío durante la noche para dar la (R)-3-(6-bromo-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina (16-2) como un sólido amarillo claro, el cual se utilizó en el siguiente paso sin mayor purificación. LC/MS: 438.2 ($M+H^+$).

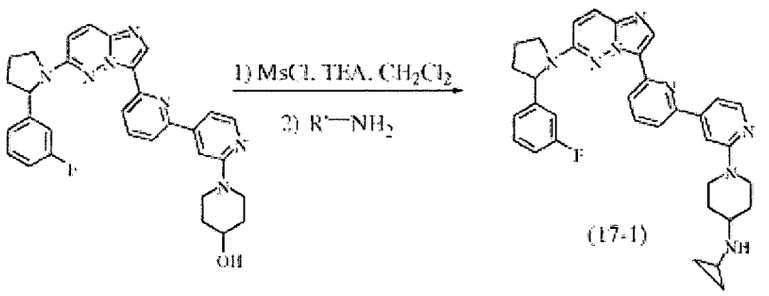
En el paso 16-3, se agregaron ácido 2-fluoro-piridin-4-il-borónico (97 por ciento) (9.6 gramos, 66 milimoles), $Pd(dppf)Cl_2$ (1.3 gramos, 1.65 milimoles), y Na_2CO_3 2N (50 mililitros, 99 milimoles) a una suspensión de (R)-3-(6-bromo-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina (16-2) (14.5 gramos, 33 milimoles) en 1,4-dioxano (250 mililitros). La mezcla se desgasificó durante 15 minutos utilizando N_2 y entonces se calentó a 110°C

durante 3 horas. La mezcla se filtró a través de un cojín de Celite, y se enjuagó con acetato de etilo (EtOAc). El filtrado se lavó con salmuera, se secó sobre Na_2SO_4, y se concentró, para dar la (R)-3-(2'-fluoro-2,4'-bipiridin-6-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina (16-3) como un aceite oscuro, el cual se utilizó en el siguiente paso sin mayor purificación. LC/MS: 455.2 ($M+H^+$).

En el paso 16-4, se agregaron fluoruro de potasio (10 gramos, 175 milimoles), y 4-hidroxi-piperidina (10.6 gramos, 105 milimoles) a una solución de (R)-3-(2'-fluoro-2,4'-bipiridin-6-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina (16-3) cruda (16.1 gramos, 35 milimoles) en sulfóxido de dimetilo (100 mililitros). La mezcla se calentó durante la noche a 120°C (aproximadamente 14 horas). La mezcla se filtró a través de un cojín de Celite y se enjuagó con EtOAc (1 litros). El filtrado se lavó con salmuera, se secó sobre Na_2SO_4, se filtró, y se concentró, para dar un aceite oscuro. La mezcla se purificó mediante cromatografía en columna (gel de sílice, CH_2Cl_2/CH_3OH, gradiente del 5 por ciento al 15 por ciento), para proporcionar el (R)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-piperidin-4-ol (16-4), el cual se trituró a partir de CH_2Cl_2, se filtró, y se secó bajo un alto vacío. ^1H RMN (400 MHz, DMSO, ppm): δ 8.30 (s, 1H), 8.22 (d, 1H, J=5.2 Hz), 8.10-8.24 (bs, 1H), 7.90-7.98 (m, 2H), 7.76-7.86 (bs, 1H), 7.52 (s, 1H), 7.40 (q, 1 H, J=7.4 Hz), 7.34 (d, 1H, J=5.2 Hz), 7.04 (t, 1H, J=8 Hz), 6.80-6.94 (bs, 1H), 5.19 (d, 1H, J=8 Hz),

4.71 (d, 1H, J=4 Hz), 4.10-4.18 (m, 2H), 3.93-4.06 (m, 1H), 3.65-3.75 (m, 2H), 3.10-3.20 (m, 2H), 1.98-2.10 (m, 2H), 1.78-1.92 (m, 3H), LC/MS: 536.2 ($M+H^+$), 1.34-1.45 (m, 2H). ^{13}C RMN (400 MHz, DMSO, ppm): 163.53, 161.11, 159.53,153.95, 151.76, 148.27 (d, J=34.7 Hz), 147.69, 147.10 (d, J=25.6 Hz), 146.92, 137.61, 133.14 (d, J=23.2 Hz), 130.34 (d, J=32.4 Hz), 126.54, 126.04, 121.56, 119.26, 118.75, 113.40 (d, J=83.6 Hz), 112.41 (d, J=86.0), 110.26, 109.86, 103.75, 66.34, 61.24, 48.37, 42.72, 35.12, 33.71, 22.65.

Esquema 17



Ejemplo 17

La (N-ciclopropil-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-piperidin-4-amina) se sintetizó como se muestra en el esquema 17.

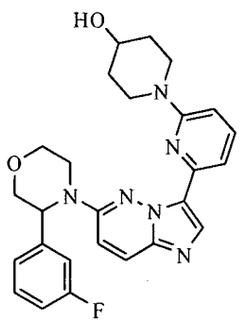
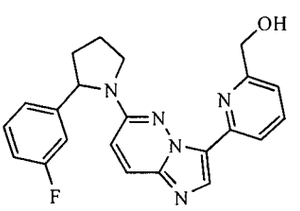
La (N-ciclopropil-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-piperidin-4-amina) se preparó de la siguiente manera. A un matraz de reacción de 20 mililitros, se le agregaron el 1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-l-il)-imidazo-[l,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-piperidin-4-ol (30 miligramos, 0.056 milimoles), y 0.8 mililitros de cloruro de metileno. Esta solución se cargó con trietil-amina (0.10 mililitros, 0.69

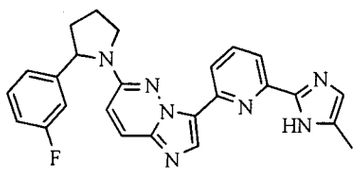
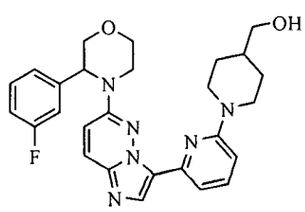
milimoles) y, mediante adición por goteo, cloruro de metan-sulfonilo (MsCl, aproximadamente 20 miligramos, 0.18 milimoles). La solución resultante se agitó durante 2 horas, seguida por apagado con agua, extracción con acetato de etilo (30 mililitros, 3 veces), y los extractos orgánicos se transfirieron a un recipiente resellable de un volumen de 10 mililitros. El residuo del recipiente se cargó con 2 mililitros de ciclopropil-amina (exceso, co-solvente), y 0.5 mililitros de tetrahidro-furano. El recipiente se selló y se calentó durante 6 horas a 90°C. Después de enfriarse, el contenido del recipiente se concentró hasta un volumen de 1 mililitro, y se sometió directamente a separación en fase inversa (gradiente, soporte C-18, del 10 al 70 por ciento, acetonitrilo : agua), para dar la (N-ciclopropil-l-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-l-il)-imidazo-[l,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-piperidin-4-amina). ^{1}H RMN (400 MHz, D_3 acetonitrilo) δ ppm 8.71 (br s, 1H), 8.41(s, 1H) 8.26 (d, J = 7.2 Hz, 1H), 7.99 (app d, J = 6.7 Hz, 2H), 7.85 (d, J = 6.2 Hz, 1H), 7.73 (br s, 1H), 7.63 (s, 1H), 7.42 (d, J = 6.4 Hz, 1H), 7.39 (app q, J = 6.8 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.05 (dt, J = 8.6, 1.9 Hz, 1H), 6.99-6.82 (m, 1H), 5.27 (d, J = 6.4 Hz, 1H), 4.54 (app d, J = 10 Hz, 2H), 4.00 (app q, J = 3.9 Hz, 1H), 3.69-3.62 (m, 1H), 3.46 (app d, J = 5.8 Hz, 1H), 2.98 (app q, J = 4.2 Hz, 2H), 2.73 (br s, 2H), 2.47-2.35 (m, 1H), 2.13 (app dd, J = 5.6 Hz, 2H), 2.08-2.03 (m, 2H),1.89-1.86 (m, 1H), 0.82-0.66 (m, 5H). LRMS observada m/z 575.3 ion mayor (Calculado para M+H, 575.3).

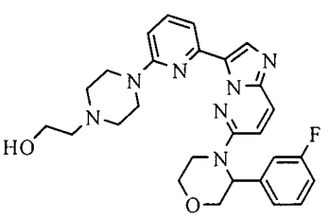
Los compuestos representativos adicionales de la fórmula (I), preparados siguiendo los procedimientos descritos anteriormente, se

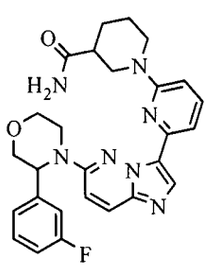
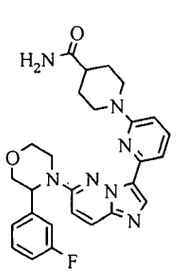
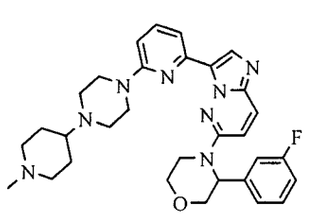
estipularon en la Tabla 7.

Tabla 7

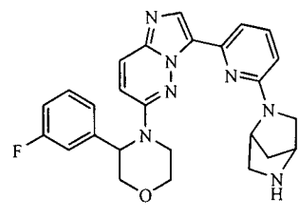
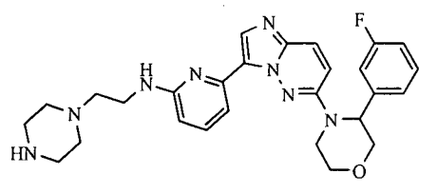
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
1		^{1}H RMN (400 MHz, MeOH-d4) d 7.99 (s, 1H), 7.71(d, 1H, J = 10.0 Hz), 7.46 (m, 2H), 7.19 (m, 1H), 7.11 (m, 3H), 6.83 (m, 1H), 6.65 (d, 1H, J = 8.0 Hz), 5.01 (t, 1H, J = 3.6 Hz), 4.10 (m, 3H), 4.00 (m, 2H), 3.77 (m, 3H), 3.59 (m,1H), 3.03 (m, 1H), 1.91 (s, 1H), 1.84 (m, 2H), 1.44 (m, 2H) MS (m/z): 474.53
2		MS (m/z): 389.42

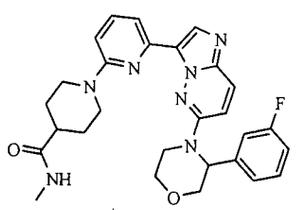
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
3		MS (m/z): 439.49
4		^{1}H RMN (400 MHz, CHCl3-d3) d 8.54(d, 1H, J = 10.0 Hz), 8.23 (s, 1H), 7.46 (m, 2H), 7.23 (m, 1H), 7.12 (d, 1H, J = 10.4 Hz), 7.05 (m, 2H), 6.91 (m, 1H), 6.65 (m, 1H), 5.09 (t, 1H, J = 2.8 Hz), 4.34 (m,2H), 4.24 (dd, 1H, J = 12.0, 2.0 Hz), 4.12 (dt, 1H, J = 11.2, 2.8 Hz), 4.05 (dd, 1H, J = 12.8, 3.6 Hz), 3.92 (dt, 1H, J = 12.8, 2.8 Hz), 3.82 (ddd, 1H, J = 11.2, 11.2, 3.2 Hz), 3.65 (m,2H), 3.48 (d, 2H, J =

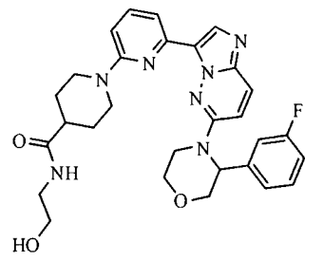
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		6.0 Hz), 3.30 (br s, 1H), 2.82 (ddd, 1H, J = 12.4, 12.4, 1.6 Hz), 1.73 (m, 1H), 1.24 (m, 3H), 0.80 (m, 1H) MS (m/z): 488.56
5		^{1}H RMN (400 MHz, CHCl3-d3) d 8. 41(d, 1H, J = 10.0 Hz), 8.20 (s, 1H), 7.64 (d, 1H, J = 7.6 Hz), 7.58 (t, 1H, J = 8.0 Hz), 7.24 (m, 1H), 7.13 (d, 1H, J = 10.0 Hz), 7.05 (m, 1H), 6.91 (m, 1H), 6.67 (d, 1H, J = 8.4 Hz), 5.09 (t, 1H, J = 2.8 Hz), 4.23 (dd, 2H, J = 12.0, 2.4 Hz), 4.12 (dt, 2H, J = 12.8, 3.2 Hz), 4.05 (dd,

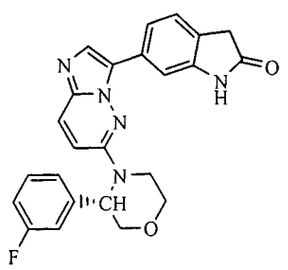
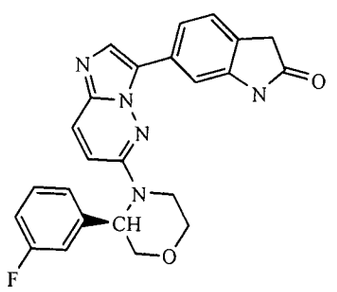
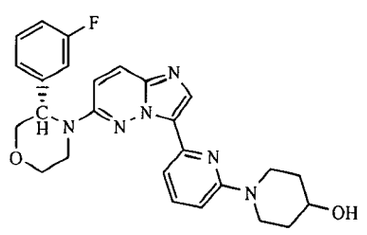
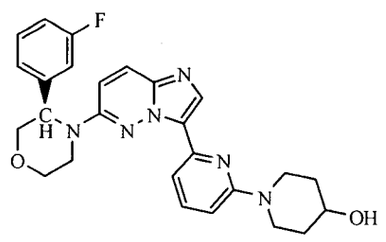
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2H, J = 12.0, 4.0 Hz), 3.99 (m, 3H), 3.90 (dt, 2H, J = 13.2, 2.8 Hz), 3.82 (ddd, 2H, J = 10.4, 10.4, 3.2 Hz), 3.66 (m,3H), 3.17(m, 3H) MS (m/z): 503.57
6		MS (m/z): 501.55
7		MS (m/z): 501.55
8		MS (m/z): 556.68

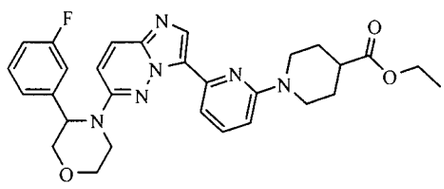
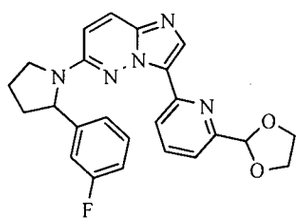
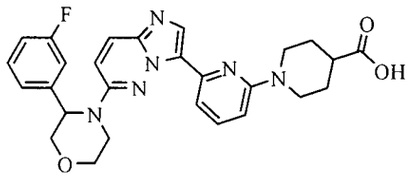
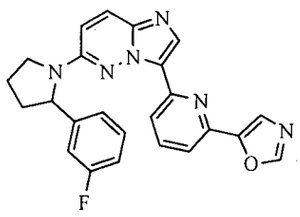
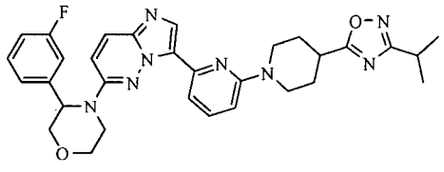
326

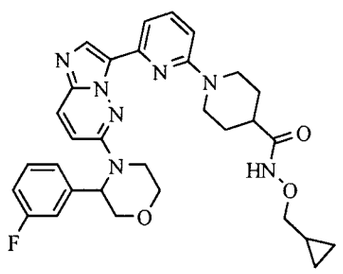
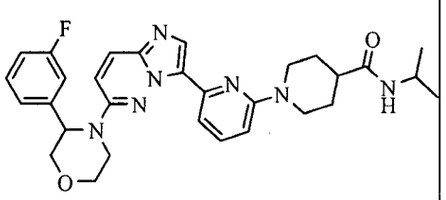
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
9		^{1}H RMN (400 MHz, MeOH-d4) d 8.19 (s, 1H), 7.74(d, 1H, J = 10.0 Hz), 7.51 (t, 1H, J = 8.8 Hz), 7.42 (ddd, 1H, J = 8.0, 8.0, 2.8 Hz), 7.17 (m, 1H), 7.08 (m, 2H), 6.84 (ddd, 1H, J = 8.4, 8.4, 2.0 Hz), 6.76 (d, 1H, J = 9.6 Hz), 6.23 (d, 1H, J = 8.0 Hz), 5.00 (m, 1H), 4.11 (dd, 1H, J = 13.2, 3.2 Hz), 4.03 (m, 2H), 3.80 (m, 3H), 3.59 (m,2H), 3.28 (d,1H, J = 9.6 Hz), 3.08 (s, 2H), 1.85 (m, 1H) MS (m/z): 471.53
10		MS (m/z): 502.59

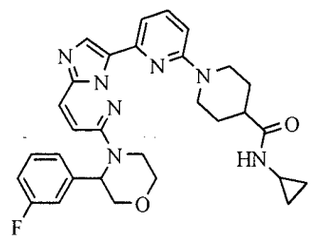
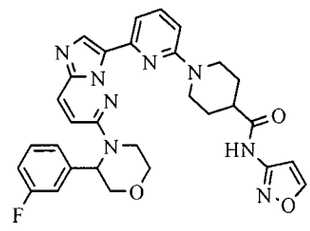
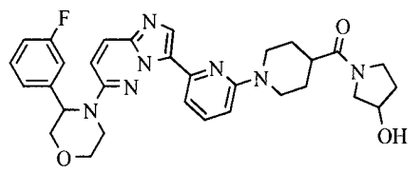
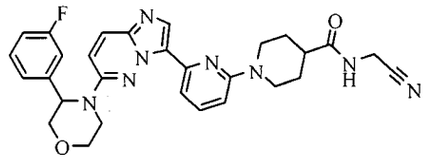
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
11		^{1}H RMN (400 MHz, MeOH-d4) d 8.10 (s, 1H), 7.82(d, 1H, J = 10.0 Hz), 7.57(m, 2H), 7.32 (m, 1H), 7.20 (m, 3H), 6.91(m, 1H), 6.76 (d, 1H, J = 8.40 Hz), 5.22 (t, 1H, J = 3.2 Hz), 4.49 (d,2H, J = 13.2 Hz), 4.20 (dd, 1H, J = 12.0, 3.2 Hz), 4.11 (m, 2H), 3.90 (m, 2H), 3.70 (m, 1H), 2.88 (ddd,2H, J = 12.4, 12.4, 2.4 Hz), 2.72 (s, 3H), 2.72 (s, 1H), 1.84 (m, 2H), 1.74 (m, 2H) MS (m/z): 515.58

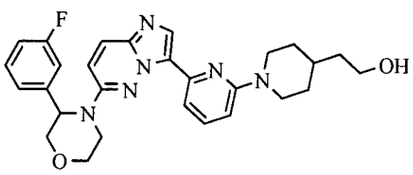
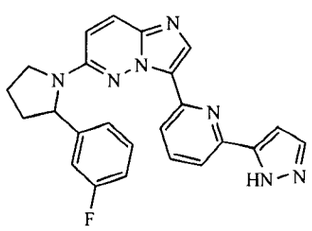
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
12		^{1}H RMN (400 MHz, MeOH-d4) d 8.18 (s, 1H), 7.73(d, 1H, J = 10.0 Hz), 7.53(d, 1H, J = 7.6 Hz), 7.45 (t, 1H, J = 8.0 Hz), 7.17 (m, 1H), 7.07(m, 2H), 6.84 (m, 1H), 6.76 (d, 1H, J = 8.0 Hz), 6.54 (d, 1H, J = 8.4 Hz), 6.16 (t, 1H, J = 4.2 Hz), 5.00 (t, 1H, J = 3.6 Hz), 4.38 (d,2H, J = 12.4 Hz), 4.11 (dd, 1H, J = 12.0, 3.6 Hz), 4.03 (m, 2H), 3.80 (m, 2H), 3.66 (t, 2H, J = 4.8), 3.60 (m, 1H), 3.37 (m,1H), 2.83 (m, 2H), 2.31 (m, 1H), 1.80 (m, 2H), 1.74 (m, 2H), 1.18 (m, 1H) MS (m/z): 545.61

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
13		MS (m/z): 429.45
14		MS (m/z): 429.45
15		MS (m/z): 474.53
16		MS (m/z): 474.53

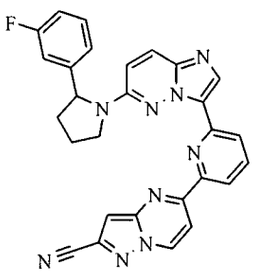
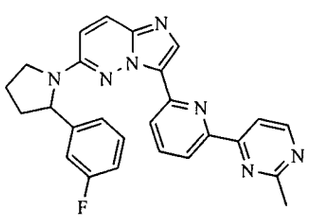
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
17		MS (m/z): 530.59
18		MS (m/z): 431.46
19		MS (m/z): 502.54
20		MS (m/z): 426.45
21		MS (m/z): 568.64

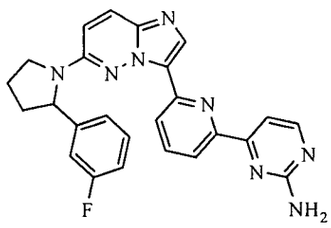
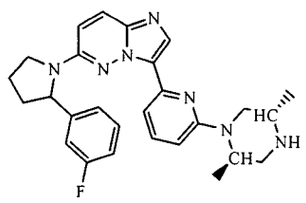
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
22		MS (m/z): 571.65
23		^{1}H RMN (400 MHz, DMSO-d6) d 8.12 (s, 1H), 8.09 (d, 1H, J = 6.0 Hz), 7.67 (d, 1H, J = 7.6 Hz), 7.56 (m, 2H), 7.09 (m, 4H), 7.04 (ddd, 1H, J = 8.4, 8.4, 2.4 Hz), 6.78 (d, 1H, J = 8.0 Hz), 5.30 (s, 1H), 4.40 (d, 2H, J = 11.6 Hz), 4.19 (dd, 1H, J = 12.0, 2.0 Hz), 4.02 (m, 3H), 3.80 (m, 2H), 3.60 (m, 1H), 2.82 (t, 2H, J = 12.0 Hz), 2.34 (m, 1H), 1.70 (m, 2H), 1.56 (m, 2H), 1.03 (d, 6H, J =

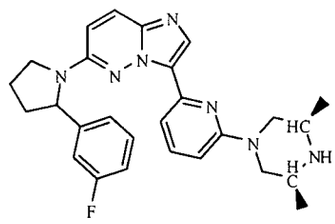
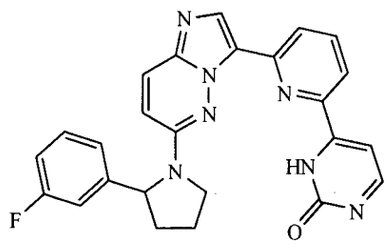
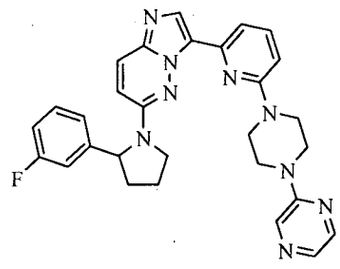
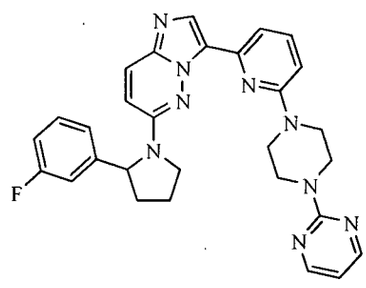
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		6.4 Hz) MS (m/z): 543.64
24		MS (m/z): 541.62
25		MS (m/z): 568.60
26		MS (m/z): 571.65
27		MS (m/z): 540.59

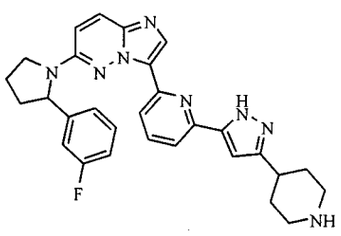
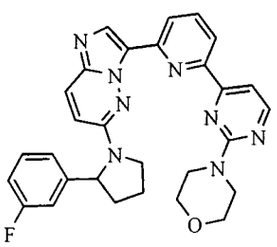
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
28		MS (m/z): 502.58
29		^{1}H RMN (400 MHz, MeOH-d4) d 8.33 (s, 1H), 8.03 (s br, 1H), 7.75 (d, 1H, J = 9.6 Hz), 7.60 (m, 2H), 7.46 (d, 1H, J = 7.6 Hz), 7.26 (m, 1H), 7.09 (d, 1H, J = 7.6 Hz), 6.91 (m, 2H), 6.73 (d, 1H, J = 2.0 Hz), 6.55 (d, 1H, J = 10.0 Hz), 5.03 (dd, 1H, J = 8.0, 2.4 Hz), 3.91 (m, 1H), 3.68 (q, 1H, J = 8.8 Hz), 2.44 (m, 1H), 2.06 (m,2H), 1.97 (m, 2H) MS (m/z): 425.46

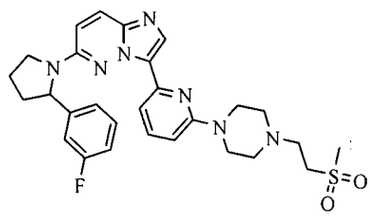
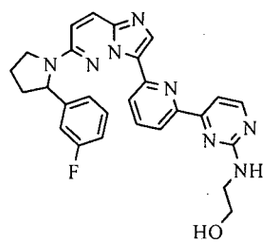
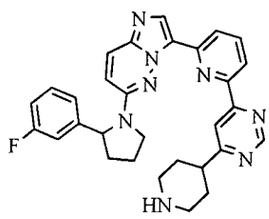
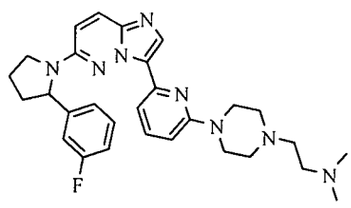
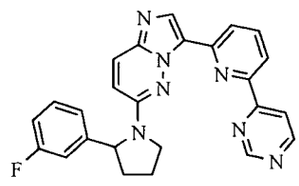
332

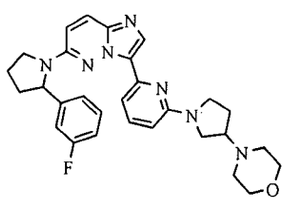
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
30		^{1}H RMN (400 MHz, DMSO-d6) d 9.01 (d, 1H, J = 4.8 Hz), 8.99 (s, 1H), 8.82 (d, 1H, J = 8.0 Hz), 8.52 (s br, 1H), 8.23 (d, 1H, J = 8.4 Hz), 8.07 (m, 3H), 7.43 (m, 1H), 7.22 (m, 2H), 7.07 (m, 2H), 5.25 (dd, 1H, J = 8.0, 2.4 Hz), 4.07 (m, 1H), 3.74 (q, 1H, J = 8.0 Hz), 2.47 (m, 1H), 2.08 (m, 2H), 1.92 (m, 1H) MS (m/z): 501.52
31		MS (m/z): 451.50

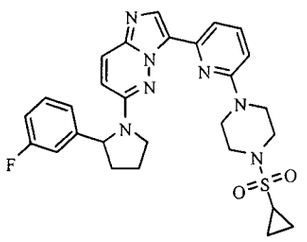
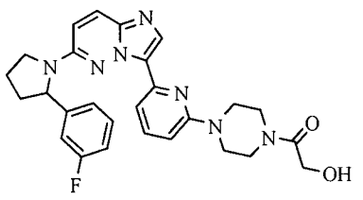
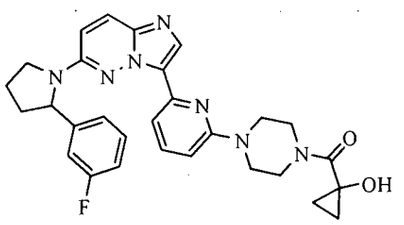
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
32		^{1}H RMN (400 MHz, DMSO-d6) d 8.42 (d, 1H, J = 4.8 Hz), 8.26 (s br, 1H), 8.31 (s, 1H), 8.15 (d, 1H, J = 8.0 Hz), 7.95 (d, 1H, J = 8.0 Hz), 7.89 (m, 1H), 7.64 (d, 1H, J = 4.8 Hz), 7.41 (ddd, 1H, J = 8.0, 6.4, 6.4 Hz), 7.20 (m, 2H), 7.05 (ddd, 1H, J = 8.4, 8.4, 2.4 Hz), 6.90 (s br, 1H), 6.76 (s, 2H), 5.22 (dd, 1H, J = 8.4, 2.8 Hz), 4.03 (m, 1H), 3.70 (q, 1H, J = 8.4 Hz), 2.47 (m, 1H), 2.06 (m, 2H), 1.89 (m, 1H) MS (m/z): 452.49
33		MS (m/z): 471.57

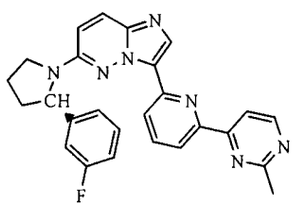
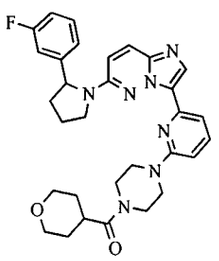
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
34		MS (m/z): 471.57
35		MS (m/z): 453.47
36		MS (m/z): 521.59
37		MS (m/z): 521.59

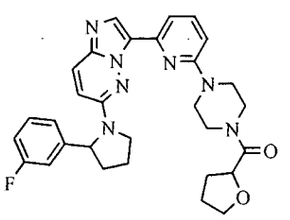
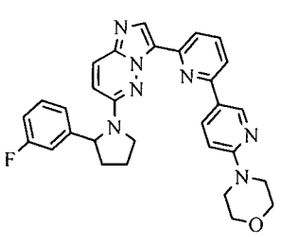
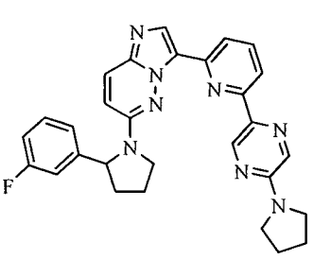
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
38		MS (m/z): 508.59
39		^{1}H RMN (400 MHz, DMSO-d6) δ 8.64 (d, 1H, J = 4.8 Hz), 8.40 (s, 1H), 8.35 (s br, 1H), 8.34 (d, 1H, J = 8.0 Hz), 8.01 (d, 1H, J = 10.0 Hz), 7.96 (m, 1H), 7.81 (d, 1H, J = 4.8 Hz), 7.46 (m, 1H), 7.26 (d, 1H, J = 7.6 Hz), 7.10 (m, 1H), 6.96 (s br, 1H), 5.27 (dd, 1H, J = 8.0, 2.8 Hz), 4.09 (m, 1H), 3.89 (t, 4H, J = 4.8 Hz), 3.78 (m, 5H), 2.53 (m, 1H), 2.12 (m, 2H), 1.95 (m, 1H) MS (m/z): 522.58

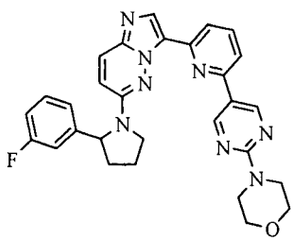
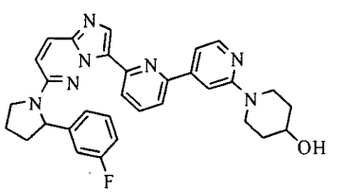
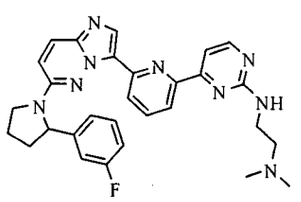
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
40		MS (m/z): 549.66
41		MS (m/z): 496.54
42		MS (m/z): 520.60
43		MS (m/z): 514.64
44		^{1}H RMN (400 MHz, DMSO-d6) δ 9.38 (d, 1H, J = 1.2 Hz), 9.05 (d, 1H, J = 5.2 Hz), 8.64 (dd, 1H, J

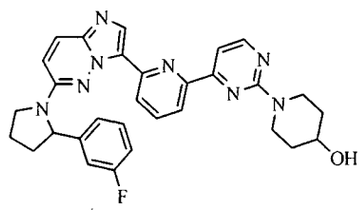
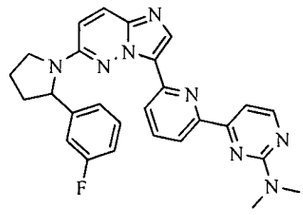
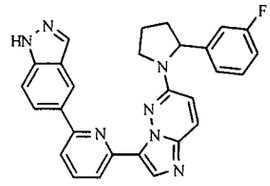
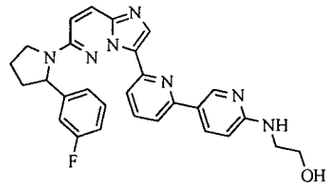
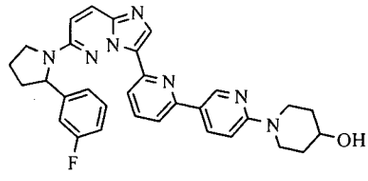
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		= 9.2, 1.2 Hz), 8.46 (s, 1H), 8.36 (d, 1H, J = 8.0 Hz), 8.01 (d, 1H, J = 10.0 Hz), 7.96 (m, 1H), 7.47 (ddd, 1H, J = 8.0, 6.4, 6.4 Hz), 7.26 (m, 3H), 7.11 (ddd, 1H, J = 8.4, 8.4, 2.4 Hz), 6.98 (s br, 1H), 5.27 (dd, 1H, J = 8.0, 2.4 Hz), 4.09 (m, 1H), 3.76 (t, 4H, J = 9.2 Hz), 2.53 (m, 1H), 2.12 (m, 2H), 1.95 (m, 1H) MS (m/z): 437.47
45		MS (m/z): 513.61

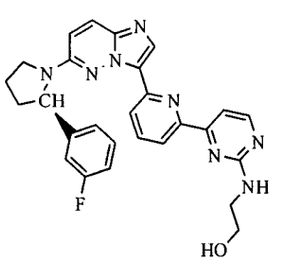
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
46		MS (m/z): 547.65
47		MS (m/z): 501.55
48		^{1}H RMN (400 MHz, DMSO-d6) d 8.10 (s, 1H), 7.89 (d, 1H, J = 6.0 Hz), 7.54 (m, 2H), 7.39 (m, 1H), 7.17 (m, 2H), 7.04 (m, 1H), 6.81 (m, 2H), 6.40 (s, 1H), 5.18 (dd, 1H, J = 8.0, 2.4 Hz), 4.00 (m, 1H), 3.69 (m, 9H), 2.45 (m, 2H), 1.87 (m, 1H), 0.96 (m, 2H), 0.80 (m, 2H)

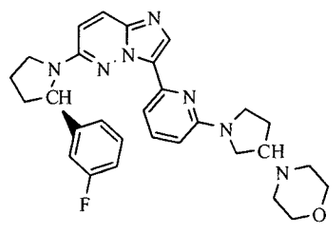
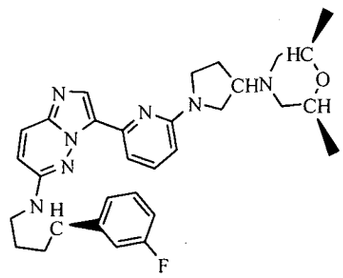
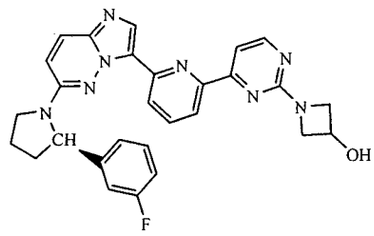
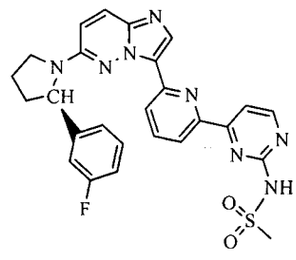
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		MS (m/z): 527.59
49		MS (m/z): 451.50
50		^{1}H RMN (400 MHz, DMSO-d6) d 8.09 (s, 1H), 7.90 (d, 1H, J = 10.0 Hz), 7.53 (m, 2H), 7.38 (m, 1H), 7.16 (m, 2H), 7.03 (m, 1h), 6.82 (s br, 1H), 6.77 (d, 1H, J = 8.4 Hz), 5.17 (dd, 1H, J = 8.4, 2.8 Hz), 4.00 (m, 1H), 3.86 (m, 2H), 3.59 (m, 8H), 3.40 (m, 3H), 2.94 (m, 1H), 2.45 (m, 1H), 2.04 (m, 2H), 1.87 (m, 1H), 1.58 (m, 4H) MS (m/z): 555.65

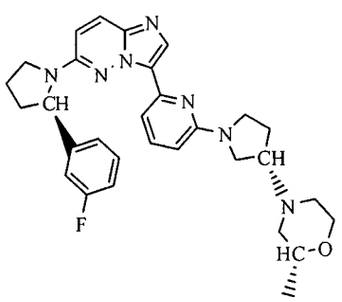
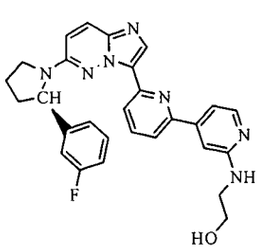
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
51		^{1}H RMN (400 MHz, DMSO-d6) d 8.15 9s, 1H), 7.95 (d, 1H, J = 9.6 Hz), 7.65 (d, 2H), 7.44 (d, 1H), 7.22 (m, 2H), 7.09 (m, 1H), 6.84 (m, 2H), 5.23 (dd, 1H, J = 8.0, 2.4 Hz), 4.78 (dd, 1H, J = 8.0, 5.6 Hz), 4.05 (m, 1H), 3.70 (m, 11H), 2.50 (m, 1H), 2.09 (m, 4H), 1.91 (m, 3H) MS (m/z): 541.62
52		MS (m/z): 521.59
53		MS (m/z): 506.58

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
54		^{1}H RMN (400 MHz, DMSO-d6) d 9.17 (s, 1H), 8.31 (s, 1H), 8.11 (s br, 1H), 7.94 9d, 1H, J = 10.0 Hz), 7.78 (m, 2H), 7.41 (m, 2H), 7.20 (m, 2H), 7.05 (m, 1H), 6.88 (m, 1H), 5.21(dd, 1H, J = 8.0, 2.4 Hz), 4.00 (m, 1H), 3.80 (m, 4H), 3.69 (m, 5H), 2.57 (m, 1H), 2.06 (m, 2H), 1.89 (m, 1H) MS (m/z): 522.58
55		MS (m/z): 536.61
56		MS (m/z): 523.61

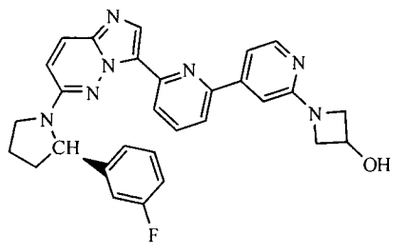
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
57		MS (m/z): 536.60
58		MS (m/z): 480.54
59		MS (m/z): 475.52
60		MS (m/z): 495.55
61		MS (m/z): 535.61

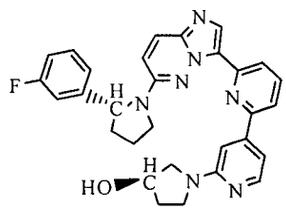
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
62		^{1}H RMN (400 MHz, DMSO-d6) d 8.46 (d, 1H, J = 4.8 Hz), 8.32 (s, 1H), 8.22 (s br, 1H), 7.95 (d, 1H, J = 6.0 Hz), 7.89 (m, 1H), 7.65 (d, 1H, J = 4.2 Hz), 7.42 (m,1H), 7.19 (m, 3H), 7.05 (ddd, 1H, J = 8.0, 8.0, 2.0 Hz), 6.90 (m, 1H), 5.20 (m, 1H), 4.74 (t, 1H, J = 5.6 Hz), 4.03 (m, 1H), 3.70 (q, 1H, J = 8.4 Hz), 3.60 (m, 2H), 3.47 (s br, 2H), 3.34 (s, 1H), 2.49 (m, 1H), 2.06 (m, 2H), 1.95 (m, 1H) MS (m/z): 496.54

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
63		MS (m/z): 513.61
64		MS (m/z): 541.66
65		MS (m/z): 508.55
66		^{1}H RMN (400 MHz, DMSO-d6) d 8.53 (d, 1H, J = 4.4 Hz), 8.22 (s, 1H), 8.16 (s br, 1H), 8.07 (d, 1H, J = 7.6 Hz), 7.82 (m, 3H), 7.29 (m, 1H), 7.07 (m, 2H), 6.91(ddd, 1H, J

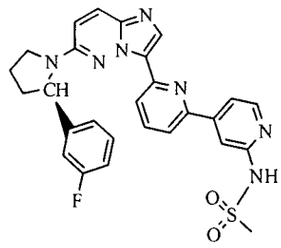
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		= 8.4, 8.4, 2.4 Hz), 6.77 (s br, 1H), 5.08 (d, 1H, J = 8.0, Hz), 3.90 (m, 1H), 3.57 (q, 1H, J = 8.0 Hz), 3.15 (s, 3H), 3.10 (m, 1H), 2.33 (m, 1H), 1.92 (m, 2H), 1.76 (m, 1H) MS (m/z): 530.58
67		MS (m/z): 527.64
68		^{1}H RMN (400 MHz, DMSO-d6) d 8.31 (s, 1H), 8.18 (s br, 1H), 8.08 (d, 1H, J = 5.2 Hz), 7.95 (d, 1H, J = 9.6 Hz), 7.79 (m, 2H), 7.40 (m,2H), 7.19 (m, 3H), 7.05 (m, 1H),

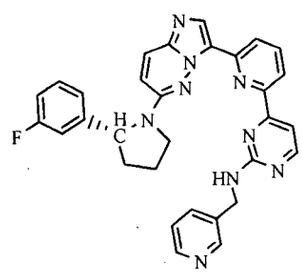
339

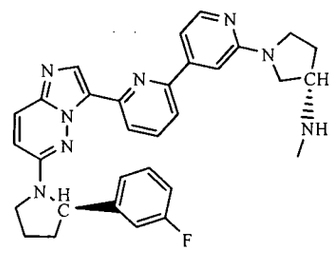
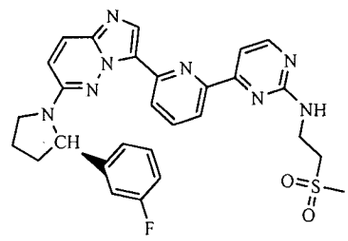
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		6.90 (m, 1H), 6.68 (t, 1H, J = 5.6 Hz), 5.21 (dd, 1H, J = 8.4, 2.4 Hz), 4.78 (t, 1H, J = 5.2 Hz), 4.03 (m, 1H), 3.69 (q, 1H, J = 8.4 Hz), 3.58 (m, 2H), 3.39 (q, 1H, J = 6.0 Hz), 3.34 (s, 1H), 2.46 (m, 1H), 2.05 (m, 2H), 1.89 (m, 1H) MS (m/z): 495.55
69		^{1}H RMN (400 MHz, DMSO-d6) d 8.29 (s, 1H), 8.19 (d, 1H, J = 5.2 Hz), 7.96 (d, 1H, J = 9.6 Hz), 7.91 (d, 1H, J = 8.0 Hz), 7.83 (m, 1H), 7.40 (m,2H), 7.20 (d, 2H, J = 7.6 Hz), 7.09 (s, 1H), 7.05 (m, 1H), 6.90 (s br,

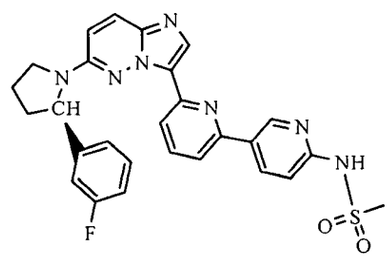
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1H), 5.67(d, 1H, J = 6.8 Hz), 5.20 (dd, 1H, J = 8.0, 2.4 Hz), 4.61 (m, 1H), 4.25 (t, 1H, J = 8.0 Hz), 4.03 (m, 1H), 3.76 (q, 1H, J = 4.0Hz), 3.70 (m, 1H), 3.34 (s, 4H), 2.49 (m, 1H), 2.06 (m, 2H), 1.89 (m, 1H) MS (m/z): 507.56
70		^{1}H RMN (400 MHz, DMSO-d6) d 8.28 (s, 1H), 8.24 (s br, 1H), 8.18 (d, 1H, J = 5.2 Hz), 7.95 (d, 1H, J = 9.6 Hz), 7.90 (d, 1H, J = 8.0 Hz), 7.82 (m, 1H), 7.40 (q, 1H, J = 8.4 Hz), 7.27 (m, 1Hz), 7.19 (d, 1H, J = 7.6 Hz) 7.14 (s, 1H), 7.05 (m, 1H),

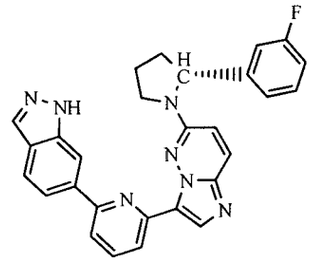
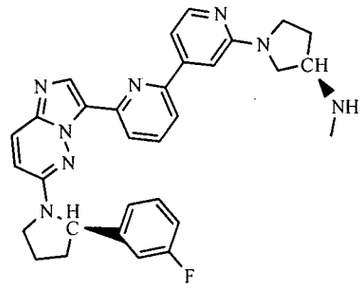
340

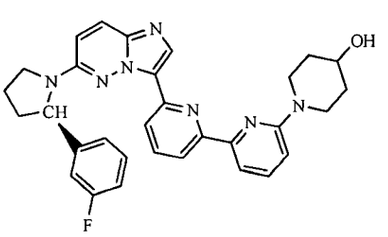
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		6.89 (s br, 1H), 5.19 (dd, 1H, J = 8.0, 2.4 Hz), 4.99 (d, 1H, J = 3.2 Hz), 4.43 (s, 1H), 4.02 (m, 1H), 3.90 (q, 1H, J = 9.2Hz), 3.58 (m, 1H), 3.42 (d, 1H, J = 10.8 Hz), 2.46 (m, 1H), 2.05 (m, 3H), 1.91 (m, 2H) MS (m/z): 521.59
71		^{1}H RMN (400 MHz, DMSO-d6) d 8.31 (d, 1H, J = 5.6 Hz), 8.29 (s, 1H), 8.25 (s br, 1H), 7.96 (d, 1H, J = 10.0 Hz), 7.87 (m, 2H), 7.73 (s, 1H), 7.60 (dd, 1H, J = 5.6, 1.2 Hz), 7.41(m, 1H), 7.20 (d, 1H, J = 8.4 Hz), 7.05 (m, 1H), 6.91 (s br, 1H), 5.21(dd,

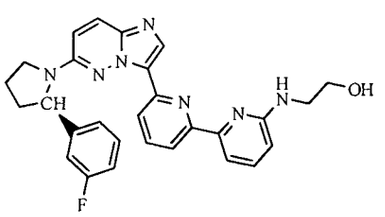
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1H, J = 8.4, 2.4 Hz), 4.03 (m, 1H), 3.71 (q, 1H, J = 8.0 Hz), 3.23 (s, 3H), 3.20 (m, 1H), 2.47 (m, 1H), 2.06 (m, 2H), 1.89 (m, 1H) MS (m/z): 529.59
72		^{1}H RMN (400 MHz, DMSO-d6) d 8.65 (s br, 1H), 8.48(d, 1H, J = 5.2 Hz), 8.44 (dd, 1H, J = 4.8, 1.6 Hz), 8.31 (s, 1H), 8.18 (d, 1H, J = 8.0 Hz), 7.95 (d, 2H, 9.6 Hz), 7.88 (m, 1H), 7.81 (m, 1H), 7.68 (d, 1H, J = 6.8 Hz), 7.39 (m, 2H), 7.19 (m, 2H), 7.05(ddd, 1H, J = 8.0, 8.0, 2.0 Hz), 6.90 (s br, 1H), 5.21 (dd, 1H, J =

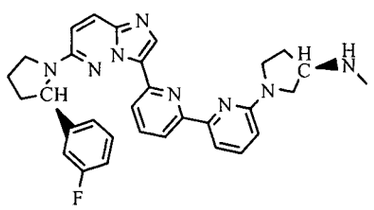
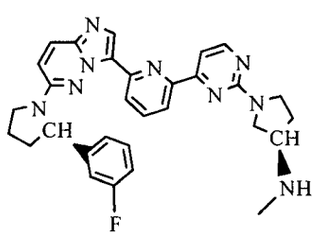
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		6.0, 1.6Hz), 4.63 (d, 2H, J = 5.6Hz), 4.03 (m 1H), 3.70 (q, 1H, J = 8.4 Hz), 3.34 (s, 1H), 2.46 (m, 1H), 2.05 (m, 2H), 1.88 (m, 1H) MS (m/z): 543.60
73		MS (m/z): 534.63
74		^{1}H RMN (400 MHz, DMSO-d6) d 8.51 (d, 1H, J = 4.8 Hz), 8.33 (s, 1H), 8.26 (s br, 1H), 7.96 (d, 1H, J = 9.6 Hz), 7.90 (m, 1H), 7.73 (d, 1H, J = 4.8 Hz), 7.45(m, 2H), 7.20 (m, 2H), 7.05(ddd, 1H, J

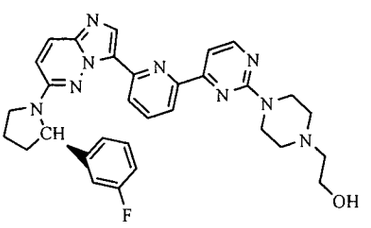
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		= 8.4, 8.4, 2.0 Hz), 6.91 (s br, 1H), 5.21 (dd, 1H, J = 8.0, 2.8 Hz), 4.04 (m, 1H),3.81 (m, 2H), 3.71 (q, 1H, J = 8.0 Hz), 3.45 (t, 2H, J = 6.8 Hz), 3.34 (s, 1H), 3.07(s, 3H), 2.46 (m, 1H), 2.06 (m, 2H), 1.89 (m, 1H) MS (m/z): 558.63
75		^{1}H RMN (400 MHz, DMSO-d6) d 8.98 (d, 1H, J = 6.0 Hz), 8.45 (dd, 1H, J= 8.8, 2.0 Hz), 8.31 (s, 1H), 8.10 (s br, 1H), 7.95 (d, 1H, J = 10.0 Hz), 7.80 (m, 2H), 7.41 (m, 1H), 7.07 (m, 2H), 6.91(ddd, 1H, J = 8.4, 8.4, 2.4 Hz), 6.77 (s br, 1H), 5.08 (dd,

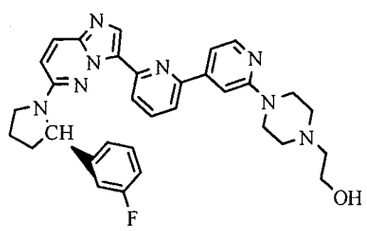
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1H, J = 8.0, 2.4 Hz), 3.90 (m, 1H), 3.57 (q, 1H, J = 8.0 Hz), 3.15 (s, 3H), 3.10 (m, 1H), 2.33 (m, 1H), 1.92 (m, 2H), 1.76 (m, 1H) MS (m/z): 529.59
76		MS (m/z): 475.52
77		^{1}H RMN (400 MHz, DMSO-d6) d 8.30 (s, 1H), 8.23 (d, 1H, J = 5.6 Hz), 8.1 (s br, 1H), 7.95 (t, 2H, J = 8.8 Hz), 7.85 (s br, 1H), 7.39 (m, 2H), 7.21 (m, 3H), 7.05 (m, 1H), 6.90(s br, 1H), 5.21 (dd,

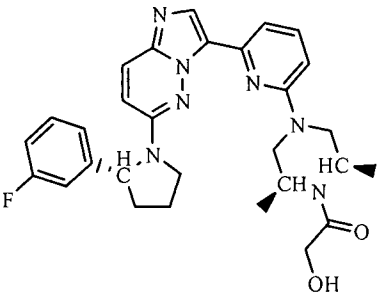
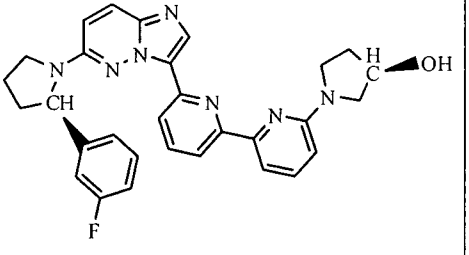
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1H, J = 8.0, 2.8 Hz), 4.03 (m, 1H), 3.80 (m, 2H), 3.67 (m, 3H), 2.61 (s, 3H), 2.47 (m, 1H), 2.35 (m, 1H), 2.20 (m, 1H), 2.06 (m, 2H), 1.89 (m, 1H), 1.18 (d, 1H, J = 6.8 Hz) MS (m/z): 534.63
78		^{1}H RMN (400 MHz, DMSO-d6) δ 8.29 (s, 1H), 8.19 (d, 1H, J = 8.0 Hz), 7.94 (d, 1H, J = 9.6 Hz), 7.84 (m, 3H), 7.68 (t, 2H, J = 8.4 Hz), 7.41 (m, 1H), 7.19 (m, 2H), 7.05 (m, 1H), 6.93 (d, 1H, J = 8.4 Hz), 6.90(s br), 5.21 (dd, 1H, J = 8.0, 2.8 Hz), 4.73 9d, 1H, J = 4.4 Hz), 4.16

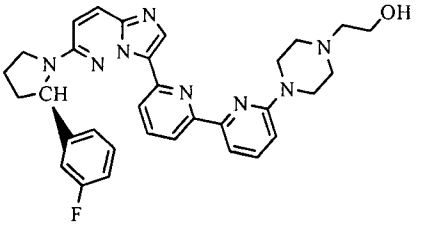
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(m,2H), 4.03 (m, 1H), 3.73 (m, 2H), 3.17 (m, 2H), 2.47 (m, 1H), 2.06 (m, 2H), 1.87 (m, 3H), 1.44 (m, 2H) MS (m/z): 535.61
79		^{1}H RMN (400 MHz, DMSO-d6) δ 8.28 (s, 1H), 8.14 (d, 1H, J = 8 Hz), 7.94 (d, 1H, 9.6 Hz), 7.82 (m, 1H), 7.68 (d, 1H, J = 7.2 Hz), 7.53 (t, 1H, J = 7.2 Hz), 7.41 (ddd, 1H, J = 8.0, 8.0, 6.4 Hz)), 7.19 (m, 2H), 7.05 (ddd, 1H, J = 8.4, 8.4, 2.0 Hz), 6.88(s br, 1H), 6.665 (t, 1H, J = 5.6 Hz), 6.58 (d, 1H, J = 8.0 Hz), 5.21 (dd, 1H, J = 8.0, 2.4 Hz), 4.79 (t, 1H,

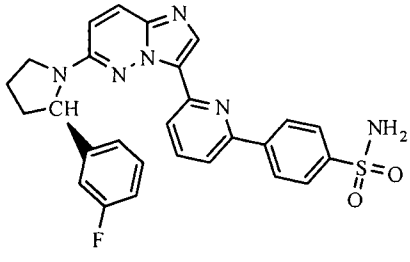
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		J = 5.6 Hz), 4.03 (m, 1H), 3.66(m, 3H), 3.46 (m, 2H), 2.45 (m, 1H), 2.06 (m, 2H), 1.89 (m, 1H) MS (m/z): 495.55
80		MS (m/z): 534.63
81		^{1}H RMN (400 MHz, DMSO-d6) δ 8.57 (s, 1H, J = 5.2 Hz, 8.39 (s, 1H), 8.36 (s, br, 1H), 8.34 (d, 1H, J = 7.6 Hz), 7.99 (m, 2H), 7.72 (d, 1H, J = 4.2 Hz), 7.47 (m, 1H), 7.26 (m, 2H), 7.11 (m, 1H), 6.96 (s br, 1H), 5.27 (dd, 1H, J = 8.0, 2.0 Hz), 4.09 (m, 1H), 3.58 (m, 4H),

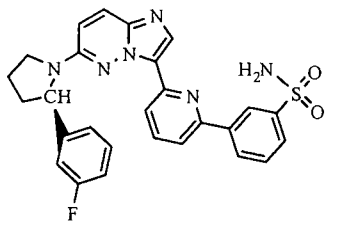
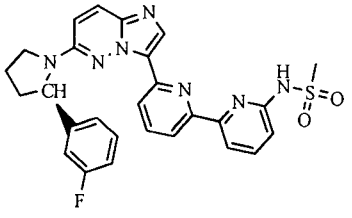
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		3.49 (s br, 1H), 3.46 (m, 2H), 2.53 (m, 1H), 2.40 (s, 3H), 2.15 (m, 3H), 1.93 (m, 2H) MS (m/z): 535.62
82		^{1}H RMN (400 MHz, DMSO-d6) δ 8.54 (d, 1H, J = 4.2 Hz), 8.33 (s, 1H), 8.25 (d, 1H, J = 7.6 Hz), 8.28 (br s, 1H), 7.94 (d, 1H, J = 10. 0 Hz), 7.89 (m, 1H), 7.68 (d, 1H, J = 4.8 Hz), 7.40 (m, 1H), 7.19 (m, 2H), 7.04 (m, 1H), 6.88 (br s, 1H), 5.20 (dd, 1H, J = 8.0, 2.8 Hz), 4.48 (br s, 1H), 4.02 (m, 1H), 3.85 (m, 4H), 3.69 (1, 1H, J = 9.2 Hz), 3.57 (t, 2H, J = 6.0 Hz), 2.50

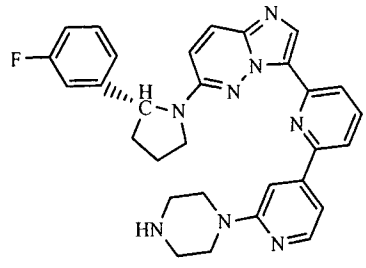
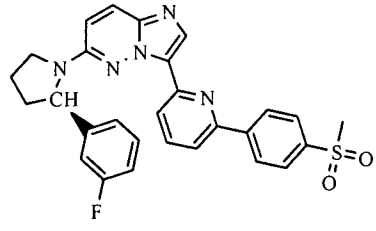
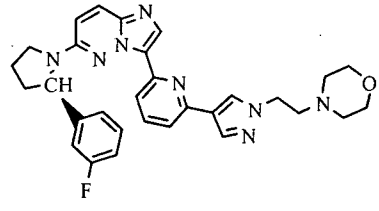
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(m, 7H), 2.05 (m, 2H), 1.89 (m, 1H) MS (m/z): 565.64
83		^{1}H RMN (400 MHz, DMSO-d6) δ 8.38 (s, 1H), 8.30 (d, 1H, J = 4.2 Hz), 8.01 (m, 2H), 7.98 (br s, 1H), 7.89(m, 1H), 7.59 (s, 1H), 7.46 (m, 2H), 7.26 (d, 2H, J = 7.6 Hz), 7.11 (m, 1H), 6.69 (br s, 1H), 5.27 (dd, 1H, J = 8.4, 2.4 Hz), 4.53 (m, 1H), 4.021(m, 1H), 3.76 (m, 1H), 3.64 (m, 6H), 2.61 (t, 4H, 4.8 Hz), 2.53 (m, 3H), 2.11 (m, 2H), 1.96 (m, 1H) MS (m/z): 564.66

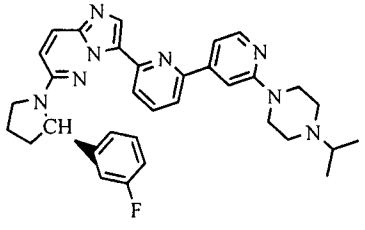
# Comp.	Estructura	Datos Físicos ¹H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
84		MS (m/z): 529.61
85		¹H RMN (400 MHz, DMSO-d6) δ 8.29 (s, 1H) 8.23 (d, 1H, J = 7.6 Hz), 8.15 (br s, 1H), 7.93 (d, 1H, J = 10.0 Hz), 7.82 (m, 1H), 7.76 (d, 1H, J = 7.2 Hz), 7.65 (t, 1H, J = 8.0 Hz), 7.40 (ddd, 1H, J = 8.0, 8.0, 6.4 Hz), 7.18 (m, 2H), 7.04 (ddd, 1H, J = 8.8, 8.0, 2.4 Hz), 6.86 (br s, 1H), 6.52 (d, 1H, J = 8.0 Hz), 5.19 (dd, 1H, J = 8.4, 2.4 Hz), 5.00 (s br, 1H), 4.44 (m, 1H), 4.02

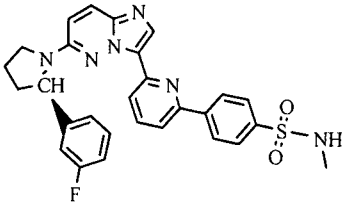
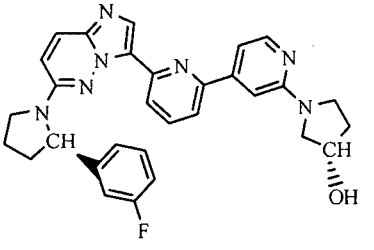
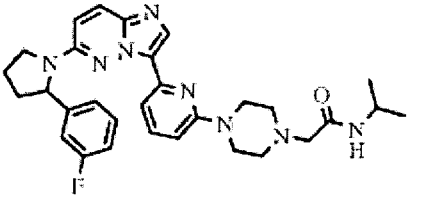
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(m, 1H), 3.69 (q, 1H, J = 7.6 Hz), 3.58 (m, 3H), 3.37 (m, 1H), 2.48 (m, 3H), 1.96 (m, 2H) MS (m/z): 521.56
86		^{1}H RMN (400 MHz, DMSO-d6) δ 8.35 (s, 1H), 8.25 (d, 1H, J = 48.0 Hz), 8.20 (s br, 1H), 7.90 (d, 1H, J = 8.0 Hz), 7.81 (br s, 1H), 7.76 (t, 1H, J = 8.0 Hz), 7.46 (q, 1H, J = 8.0 Hz), 7.25 (m, 2H), 7.11 (m, 1H), 6.97 (d, 1H, J = 8.4 Hz), 6.92 (br s, 1H), 5.26 (d, 1H, J = 8.0 Hz), 4.54 (m, 1H), 4.08 (m, 1H), 3.67 (m, 7H), 2.63 (t, 4H, J = 4.2 Hz), 2.52 (t, 3H, J = 6.4 Hz),

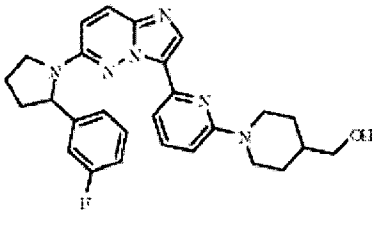
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2.11 (m, 2H), 1.96 (m, 1H) MS (m/z): 564.66
87		^{1}H RMN (400 MHz, DMSO-d6) δ 8.44 (d, 1H, 8.0 Hz), 8.40 (s, 1H), 8.00(m, 3H), 7.91 (s br, 1H), 7.76 (m, 1H), 7.52 (s, 2H), 7.46 (m, 1H), 7.27 (d, 2H, J = 7.6 Hz), 7.11 (m, 1H), 6.97 (s br, 1H), 5.28 (dd, 1H, J = 8.4, 2.4 Hz), 4.20 (dd, 1H, J = 6.0, 3.2 Hz), 4.10 (m, 1H), 3.77 (1, 1H, J = 8.0 Hz), 2.60 (s, 1H), 2.53 (m, 1H), 2.12 (m, 2H), 1.95 (m, 1H) MS (m/z): 514.57

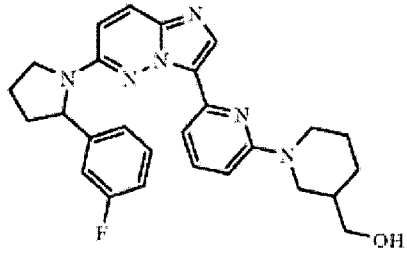
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
88		MS (m/z): 514.57
89		^{1}H RMN (400 MHz, DMSO-d6) δ 8.40 (s, 1H), 8.23 (d, 1H, J = 7.6 Hz), 8.19 (d, 1H, J = 7.6 Hz), 8.10 (d, 1H, J = 8.0 Hz), 7.95 (m, 2H), 7.48 (ddd, 1H, J = 8.0, 6.4, 6.4 Hz), 7.25 (m, 3H), 7.10 (ddd, 1H, J = 8.8, 8.8, 2.4 Hz), 7.03 (d, 1H, J = 8.0 Hz), 6.95 (s br, 1H), 5.26 (dd, 1H, J = 8.4, 2.4 Hz), 4.09 (m, 1H), 3.75 (q, 1H, J = 8.4 z), 3.51 (s, 3H), 2.55 (m, 1H), 2.11 (m, 2H), 1.91 (m, 1H) MS (m/z): 529.59

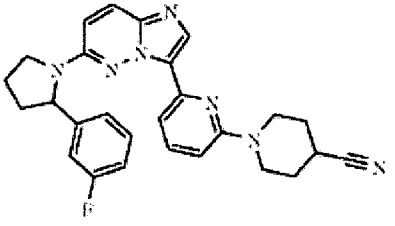
# Comp.	Estructura	Datos Físicos ¹H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
90		MS (m/z): 520.60
91		MS (m/z): 513.59
92		¹H RMN (400 MHz, DMSO-d6) δ 8.49 (s, 1H), 8.33 (s, 1H), 8.14 (s, 1H), 8.05 (s br, 1H), 7.99 (d, 1H, J = 9.6 Hz), 7.77 (m, 1H), 7.56 (d, 1H, J = 7.6 Hz), 7.45 (m, 1H), 7.24 (m, 2H), 7.10 (m, 1H), 6.95 (s br, 1H), 5.26 (dd, 1H, J = 8.0, 2.8 Hz), 4.34 (t, 2H, J = 7.2 Hz), 4.08

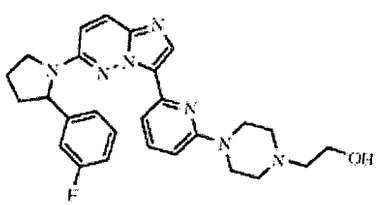
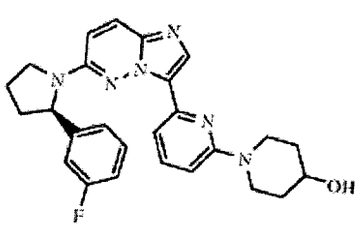
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(m, 1H), 3.75 (q, 1H, J = 8.4 z), 3.62 (t, 4H, J = 4.2 Hz), 2.83 (t, 2H, J = 6.8 Hz), 2.55 (m, 4H), 2.11 (m, 2H), 1.91 (m, 1H) MS (m/z): 538.62
93		^{1}H RMN (400 MHz, DMSO-d6) δ 8.38 (s, 1H), 8.29 (d, 1H, J = 4.2 Hz), 8.20 (s br, 1H), 8.01 (m, 2H), 7.90 (m, 1H), 7.59 (s, 1H), 7.46 (m, 2H), 7.26 (d, 2H, J = 7.6 Hz), 7.11 (m, 1H), 6.96 (s br, 1H), 5.27 (dd, 1H, J = 8.0, 2.8 Hz), 4.09 (m, 1H), 3.76 (m, 1H), 3.64 (m, 3H), 3.40 (s, 2H), 2.76 (m, 1H), 2.64 (m, 3H), 2.53 (m, 1H), 2.12

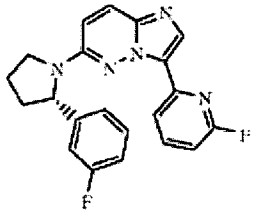
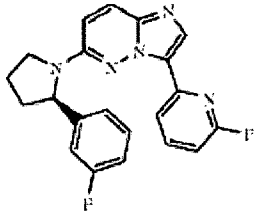
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(m, 2H), 1.95 (m, 1H), 1.08 (d, 6H, J = 6.4 Hz) MS (m/z): 562.68
94		MS (m/z): 528.60
95		MS (m/z): 521.59
96		^{1}H RMN (DMSO-d6) 8.07 (s, 1H), 7.88 (d, 1H), 7.50-7.58 (bs, 1H), 7.42-7.48 (bs, 1H), 7.35-7.40 (m, 1H), 7.13-7.17 (m, 2H), 7.01-7.05 (m, 1H), 6.78-6.85 (bs, 1H), 6.73 (d, 1H), 5.15-5.18 (q, 1H), 3.96-4.01 (m, 1H),

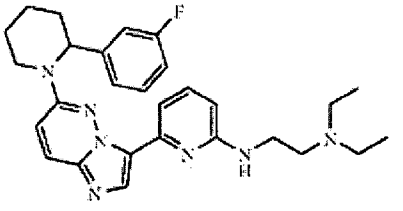
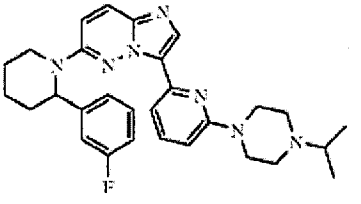
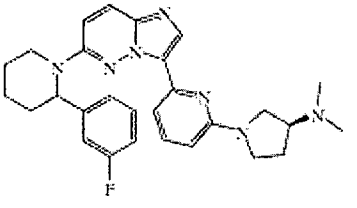
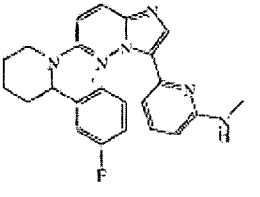
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		3.87-3.94 (m, 1H), 3.64-3.70 (m, 1H), 3.54-3.60 (bs, 4H), 2.91-2.96 (bs, 2H), 2.50-2.60 (bs, 4H), 2.45-2.50 (m, 1H), 2.00-2.06 (m, 2H), 1.84-1.90 (m, 1H), 1.08 (d, 6H). MS (m/z): 543.7
97		^{1}H RMN (DMSO-d6) 8.04 (s, 1H), 7.87 (d, 1H), 7.40-7.50 (m, 2H), 7.35-7.40 (m, 1H), 7.13-7.17 (m, 2H), 7.01-7.05 (m, 1H), 6.76-6.85 (bs, 1H), 6.72 (d, 1H), 5.14-5.17 (q, 1H), 4.46 (t, 1H), 4.37 (d, 2H), 3.95-4.01 (m, 1H), 3.64-3.69 (q, 1H), 3.27 (t, 2H), 2.74-2.81 (m, 2H), 2.45-2.50 (m,

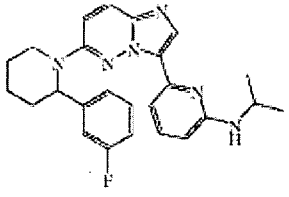
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1H), 2.00-2.06 (m, 2H), 1.84-1.89 (m, 1H), 1.58-1.64 (m, 1H), 1.08-1.17 (m, 2H). MS (m/z): 473.6
98		^{1}H RMN (DMSO-d6) 8.05 (s, 1H), 7.88 (d, 1H), 7.40-7.50 (m, 2H), 7.34-7.40 (m, 1H), 7.13-7.17 (m, 1H), 7.00-7.05 (m, 1H), 6.76-6.85 (bs, 1H), 6.69 (t, 1H), 5.15-5.18 (q, 1H), 4.54-4.57 (m, 1H), 4.34 (d, 1H), 4.22 (d, 1H), 3.96-4.02 (m, 1H), 3.64-3.70 (q, 1H), 3.28-3.37 (m, 2H), 2.81-2.88 (m, 1H), 2.59 (t, 1H), 2.45-2.50 (m, 1H), 2.00-2.08 (m, 2H), 1.84-1.90 (m, 1H), 1.72-1.77 (m, 1H),

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1.66-1.72 (m, 1H), 1.58-1.65 (m, 1H), 1.40-1.59 (m, 1H), 1.14-1.22 (m, 1H). MS (m/z): 473.6
99		^{1}H RMN (DMSO-d6) 8.07 (s, 1H), 7.88 (d, 1H), 7.41-7.60 (m, 2H), 7.34-7.40 (m, 1H), 7.12-7.18 (m, 2H), 7.00-7.15 (m, 1H), 6.78-6.85 (bs, 1H), 6.77 (d, 1H), 5.15-5.18 (q, 1H), 3.96-4.01 (m, 1H), 3.83-3.89 (m, 2H), 3.64-3.70 (q, 1H), 3.09-3.14 (m, 1H), 2.45-2.50 (m, 1H), 2.00-2.06 (m, 2H), 1.94-1.97 (m, 2H), 1.84-1.89 (m, 1H), 1.71-1.77 (m, 2H). MS (m/z): 468.5

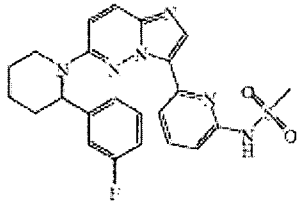
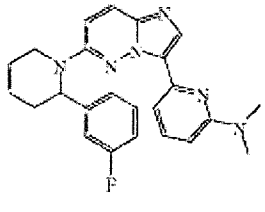
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
100		^{1}H RMN (DMSO-d6) 8.05 (s, 1H), 7.88 (d, 1H), 7.42-7.60 (m, 2H), 7.35-7.40 (m, 1H), 7.13-7.17 (m, 2H), 7.00-7.05 (m, 1H), 6.75-6.85 (bs, 1H), 6.72 (d, 1H), 5.14-5.18 (q, 1H), 4.43 (t, 1H), 3.96-4.01 (m, 1H), 3.63-3.70 (q, 1H), 3.47-3.57 (m, 6H), 2.50-2.55 (m, 4H), 2.40-2.50 (m, 3H), 2.00-2.06 (m, 2H), 1.84-1.89 (m, 1H). MS (m/z): 488.6
101		^{1}H RMN ($CDCl_3$-d6) δ 8.24 (s, 1H), 7.69 (d, 1H), J = 9.6 Hz), 7.55-7.63 (m, 1H), 7.43 (t, 1H), 7.25-7.33 (m, 1H), 7.05 (d,

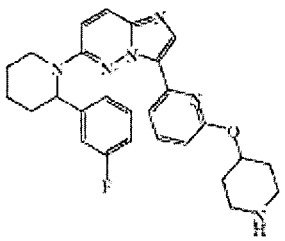
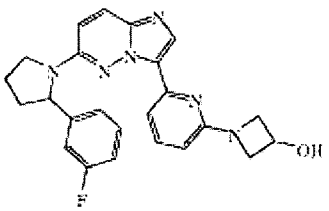
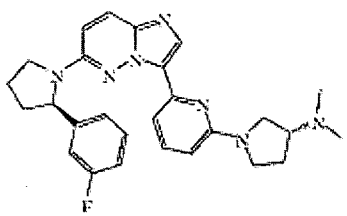
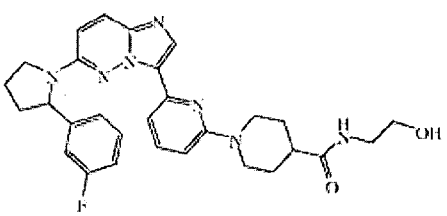
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1H), J = 7.6 Hz), 6.90-7.00 (m, 2H), 6.59 (d, 1H, J = 8.4 Hz), 6.51 (d, 1H, J = 9.6 Hz), 5.04-5.11 (m, 1H), 4.13-4.22 (m, 2H), 3.90-4.00 (m, 2H), 3.69-3.78 (, 1H), 3.13-3.22 (m, 2H), 2.42-2.54 (m, 1H), 2.06-2.20 (m, 2H), 1.96-2.05 (m, 3H), 1.55-1.62 (m, 2H). MS (m/z): 459.5
102		MS (m/z): 378.4
103		MS (m/z): 378.4

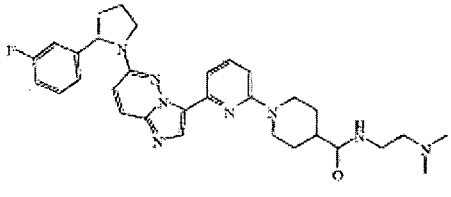
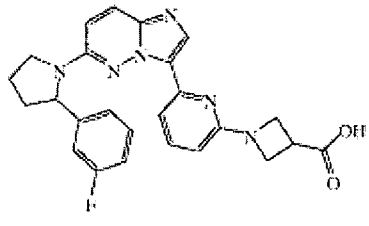
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
104		MS (m/z): 488.6
105		MS (m/z): 500.6
106		MS (m/z): 486.6
107		^{1}H RMN (DMSO-d6) δ 8.06 (s, 1H), 7.75 (s, 1H), 7.51 (d, 1H), 7.32-7.40 (m, 2H), 7.22 (d, 1H), 7.14 (d, 2H), 6.99-7.05 (m, 1H), 6.45-6.50 (m, 1H), 6.35 (d, 1H), 4.14-4.21 (m, 1H), 3.30-3.39 (m, 2H), 2.82 (d, 3H),

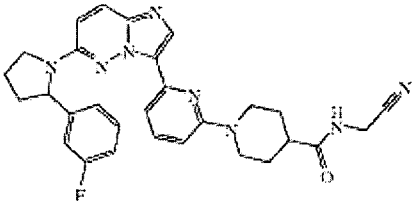
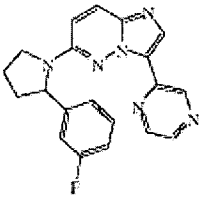
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2.17-2.26 (m, 1H), 2.00-2.10 (m, 1H), 1.56-1.83 (m, 3H), 1.35-1.50 (m, 1H). MS (m/z): 403.5
108		^{1}H RMN (DMSO-d6) δ 8.02 (s, 1H), 7.90 (d, 1H), 7.46 (d, 1H), 7.30-7.40 (m, 2H), 7.21 (d, 1H), 7.13 (d, 2H), 6.98-7.06 (m, 1H), 6.30-6.36 (m, 2H), 4.12-4.20 (m, 1H), 4.02-4.10 (m, 1H), 3.30-3.38 (m, 2H), 2.18-2.26 (m, 1H), 2.00-2.10 (m, 1H), 1.56-1.84 (m, 3H), 1.36-1.48 (m, 1H), 1.17 (d, 6H). MS (m/z): 531.5

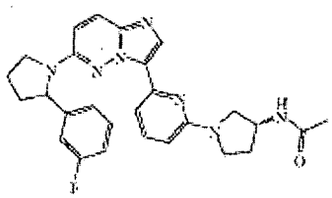
352

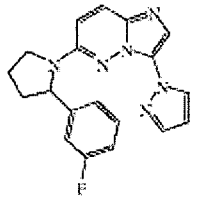
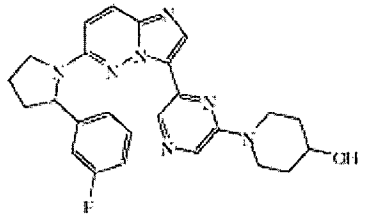
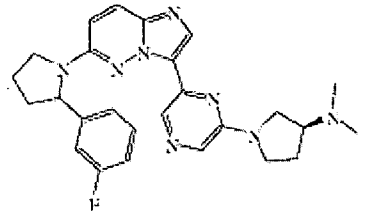
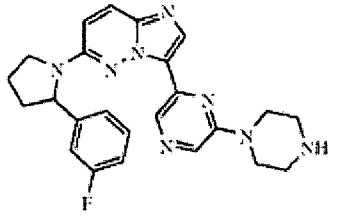
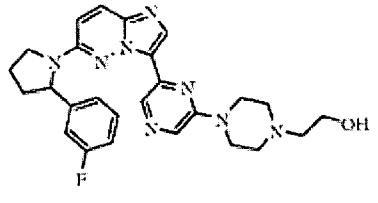
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
109		^{1}H RMN (DMSO-d6) δ 10.63 (s, 1H), 8.06 (s, 1H), 7.97 (s, 1H), 7.94 (d, 1H), 7.72 (t, 1H), 7.33-7.40 (m, 1H), 7.25 (d, 1H), 7.12-7.18 (m, 2H), 6.99-7.05 (m, 1H), 6.80 (d, 1H), 4.15-4.22 (m, 1H), 3.42 (s, 3H), 3.35-3.42 (m, 2H), 2.17-2.26 (m, 2H), 2.01-2.14 (m, 1H), 1.57-1.85 (m, 3H), 1.36-1.49 (m, 1H). MS (m/z): 467.5
110		MS (m/z): 417.5

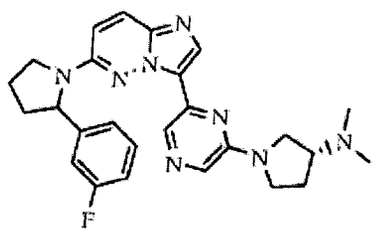
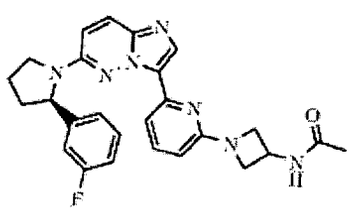
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
111		MS (m/z): 473.6
112		MS (m/z): 431.5
113		MS (m/z): 472.6
114		^{1}H RMN (DMSO-d6) 8.05 (s, 1H), 7.88 (d, 1H, J = 9.6 Hz), 7.81 (t, 1H, J = 5.6 Hz), 7.34-7.58 (m, 3H), 7.10-7.18 (m, 2H), 7.00-7.06 (m, 1H), 6.76-6.86 (bs, 1H), 6.74 (d, 1H, J = 8.8 Hz), 5.14-5.19 (m, 1H), 4.64 (t, 1H, J =

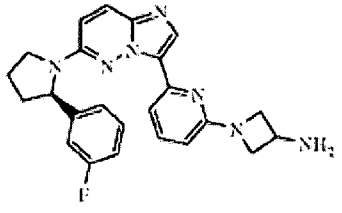
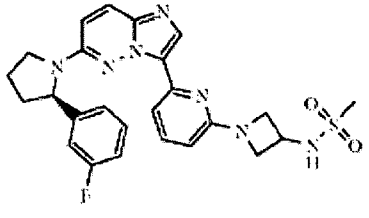
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		5.6 Hz), 4.33-4.42 (m, 2H), 3.95-4.02 (m, 1H), 3.62-3.71 (m, 1H), 3.34-3.42 (m, 2H), 3.07-3.13 (m, 2H), 2.76-2.86 (m, 2H), 2.44-2.50 (m, 1H), 2.32-2.44 (m, 1H), 2.00-2.10 (m, 2H), 1.84-1.91 (m, 1H), 1.67-1.78 (m, 2H), 1.46-1.60 (m, 2H). MS (m/z): 530.6
115		MS (m/z): 557.7
116		MS (m/z): 459.5

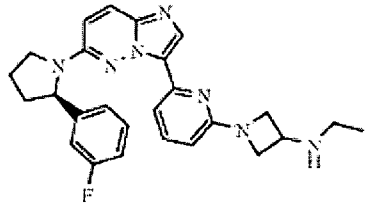
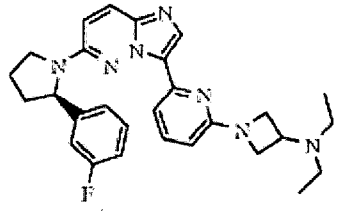
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
117		MS (m/z): 525.6
118		^{1}H RMN (DMSO-d6) 9.30-9.60 (bs, 1H), 8.63-8.66 (m, 1H), 8.52 (d, 1H, J = 12.4 Hz), 8.16 (s, 1H), 7.95 (d, 1H, J = 10 Hz), 7.32-7.40 (m, 1H), 7.11-7.17 (m, 2H), 6.98-7.06 (m, 1H), 6.78-6.92 (bs, 1H), 5.19-5.24 (m, 1H), 3.98-4.05 (m, 1H), 3.64-3.74 (m, 1H), 2.44-2.50 (m, 1H), 2.00-2.10 (m, 2H), 1.85-1.93 (m, 1H). MS (m/z): 361.4

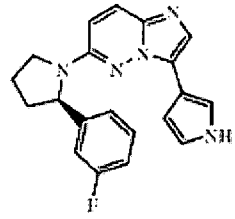
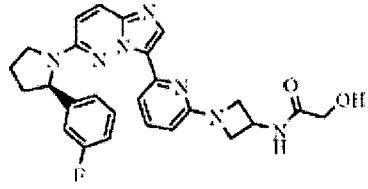
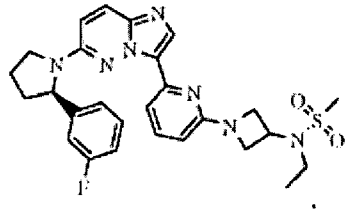
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
119		^{1}H RMN (DMSO-d6) 8.16 (d, 1H, J = 6.8 Hz), 8.04 (s, 1H), 7.87 (d, 1H, J = 9.6 Hz), 7.44-7.60 (bs, 1H), 7.34-7.44 (m, 2H), 7.12-7.20 (m, 2H), 7.00-7.06 (m, 1H), 6.72-6.90 (bs, 1H), 6.36 (d, 1H, J = 8.4 Hz), 5.14-5.20 (m, 1H), 4.30-4.40 (m, 1H), 3.96-4.02 (m, 1H), 3.61-3.72 (m, 2H), 3.42-3.60 (m, 2H), 3.24-3.30 (m, 1H), 2.42-2.50 (m, 1H), 2.10-2.10 (m, 1H), 2.00-2.10 (m, 2H), 1.82-1.90 (m, 2H), 1.81 (s, 3H). MS (m/z): 486.6

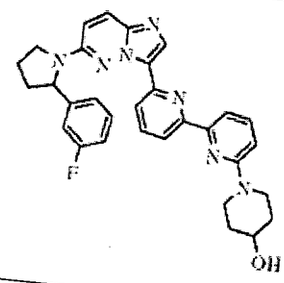
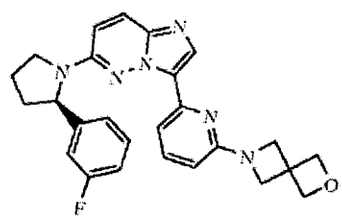
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
120		MS (m/z): 349.4
121		MS (m/z): 460.5
122		MS (m/z): 473.6
123		MS (m/z): 445.5
124		MS (m/z): 489.6

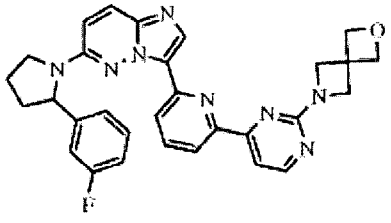
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
125		^{1}H RMN (DMSO-d6) 8.70-8.88 (bs, 1H), 8.12 (s, 1H), 7.86-7.90 (m, 2H), 7.34-7.39 (m, 1H), 7.04-7.15 (m, 2H), 7.00-7.06 (m, 1H), 6.65-6.82 (m, 1H), 5.17-5.23 (m, 1H), 3.95-4.05 (m, 1H), 3.75-3.83 (m, 1H), 3.64-3.74 (m, 2H), 3.36-3.45 (m, 1H), 3.15-3.23 (m, 1H), 2.75-2.85 (m, 1H), 2.42-2.50 (m, 1H), 2.24 (s, 6H), 2.13-2.22 (m, 1H), 1.95-2.08 (m, 2H), 1.75-1.92 (m, 2H). MS (m/z): 473.6
126		MS (m/z): 472.5

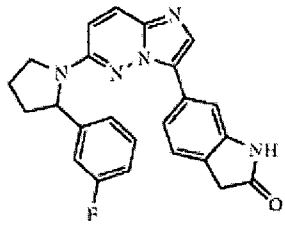
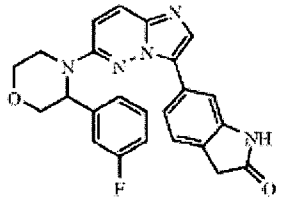
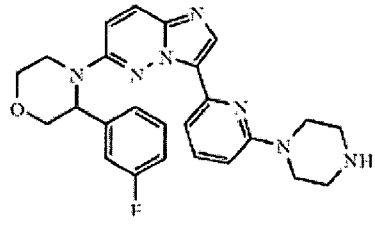
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
127		^{1}H RMN (DMSO-d6) 8.01 (s, 1H), 7.88 (d, 1H, J = 10 Hz), 7.46-7.62 (bs, 1H), 7.32-7.44 (m, 2H), 7.12-7.18 (m, 2H), 7.00-7.06 (m, 1H), 6.72-6.90 (bs, 1H), 6.27 (d, 1H, J = 8 Hz), 7.13-5.20 (m, 1H), 4.09-4.16 (m, 2H), 3.95-4.03 (m, 1H), 3.76-3.85 (m, 1H), 3.62-3.71 (m, 1H), 3.51-3.57 (m, 2H), 2.41-2.50 (m, 1H), 2.00-2.10 (m, 2H), 1.83-1.90 (m, 1H). MS (m/z): 430.5
128		^{1}H RMN (DMSO-d6) 8.03 (s, 1H), 7.89 (d, 1H, J = 10 Hz), 7.83 (d, 1H, J =8 Hz), 7.50-7.62 (bs, 1H),

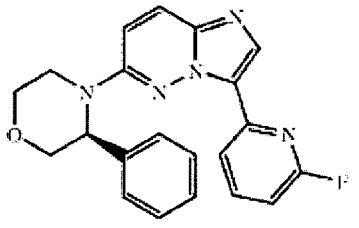
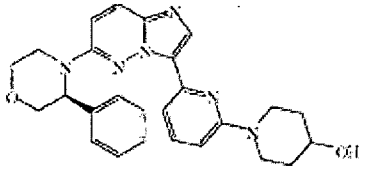
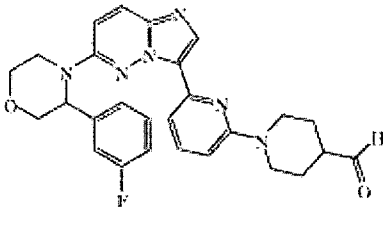
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		7.41-7.50 (m, 1H), 7.34-7.42 (m, 1H), 7.12-7.18 (m, 2H), 7.00-7.06 (m, 1H), 6.78-6.90 (bs, 1H), 6.32 (d, 1H, J = 8.2 Hz), 5.04-5.20 (m, 1H), 4.24-4.36 (m, 3H), 3.95-4.02 (m, 1H), 3.77-3.85 (m, 2H), 3.60-3.71 (m, 1H), 2.95 (s, 3H), 2.42-2.50 (m, 1H), 2.00-2.07 (m, 2H), 1.82-1.90 (m, 1H). MS (m/z): 508.6
129		MS (m/z): 458.5
130		MS (m/z): 458.6

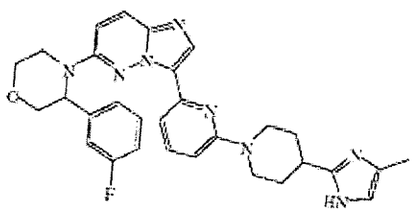
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
131		MS (m/z): 348.4
132		MS (m/z): 488.5
133		^{1}H RMN (DMSO-d6) 8.03 (s, 1H), 7.88 (d, 1H, J = 10 Hz), 7.52-7.64 (bs, 1H), 7.42-7.50 (m, 1H), 7.32-7.42 (m, 1H), 7.12-7.18 (m, 2H), 7.00-7.06 (m, 1H), 6.74-6.90 (bs, 1H), 6.34 (d, 1H, J = 8 Hz), 5.12-5.2 (m, 1H), 4.62-4.70 (m, 1H), 4.22-4.32 (m, 2H), 3.94-4.02 (m, 3H), 3.62-3.70 (m, 1H), 3.30-3.38 (m, 2H),

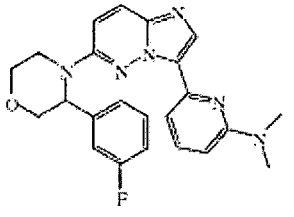
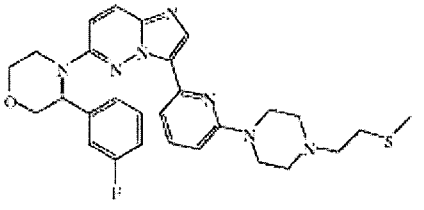
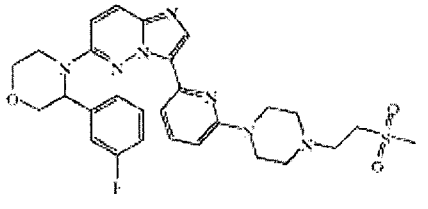
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2.95 (s, 3H), 2.42-2.50 (m, 1H), 1.98-2.08 (m, 2H), 1.82-1.90 (m, 1H), 1.20 (t, 3H). MS (m/z): 536.6
134		MS (m/z): 536.6
135		^{1}H RMN (DMSO-d6) 8.02 (s, 1H), 7.88 (d, 1H, J = 10 Hz), 7.48-7.62 (bs, 1H), 7.40-7.47 (m, 1H), 7.33-7.40 (m, 1H), 7.12-7.17 (m, 2H), 6.99-7.06 (m, 1H), 6.75-6.87 (bs, 1H), 6.29 (d, 1H, J = 8.4 Hz), 5.13-5.18 (q, 1H), 4.72 (s, 4H), 4.12 (s, 4H), 3.94-4.03 (m, 1H), 3.60-

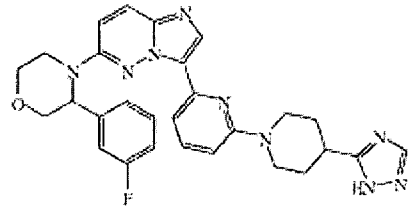
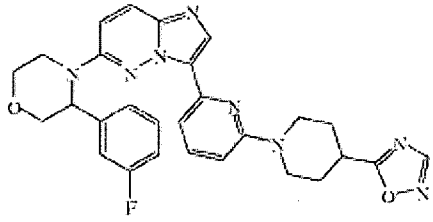
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		3.70 (m, 1H), 2.40-2.48 (m, 1H), 1.98-2.06 (m, 2H), 1.82-1.90 (m, 1H). MS (m/z): 457.5
136		^{1}H RMN (DMSO-d6) 8.52 (d, 1H, J = 5.2 Hz), 8.32 (s, 1H), 8.21 (d, 1H, J = 7.6 Hz), 7.94 (d, 1H, J = 10 Hz), 7.86-7.92 (m, 1H), 7.74 (d, 1H, J = 4.8 Hz), 7.36-7.44 (m, 1H), 7.14-7.22 (m, 2H), 7.00-7.08 (m, 1H), 6.82-6.96 (bs, 1H), 5.17-5.23 (q, 1H), 4.76 (s, 4H), 4.29 (s, 4H), 3.98-4.06 (m, 1H), 3.64-3.74 (m, 1H), 2.43-2.50 (m, 1H), 2.00-2.10 (m, 2H), 1.84-1.92 (m, 1H).

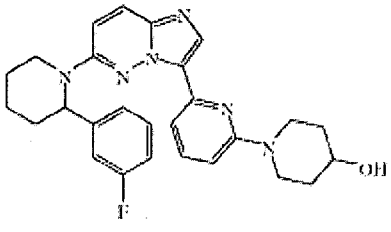
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		MS (m/z): 535.6
137		MS (m/z): 414.4
138		^{1}H RMN metanol-d4, d (ppm) 8.05 (b, 2H), 7.65 (b, 1H), 7.46 (s, 1H), 7.38 (m, 1H), 7.28 (m, 1H), 7.18 (m, 1H), 7.10 (m, 2H), 6.87 (td, 1H), 5.20 (s, 1H), 4.18 (dd, 1H), 4.02 (m, 3H), 3.76 (td, 1H), 3.60 (m, 1H), 3.53 (s, 2H). MS (m/z): 430.4
139		MS (m/z): 460.5

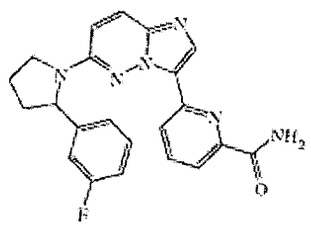
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
140		MS (m/z): 376.4
141		^{1}H RMN metanol-d4, d (ppm) 7.98 (s, 1H), 7.68 (d, 1H), 7.52 (d, 1H), 7.44 (t, 1H), 7.31 (m, 2H), 7.19 (t, 2H), 7.09 (m, 2H), 6.64 (d, 1H), 5.09 (t, 1H), 4.11 (m, 3H), 4.01 (m, 2H), 3.74 (m, 3H), 3.63 (m, 1H), 3.03 (m, 2H), 1.83 (m, 2H), 1.41 (m, 2H). MS (m/z): 457.5
142		^{1}H RMN metanol-d4, d (ppm) 8.12 (s, 1H), 7.85 (m, 1H), 7.60 (m, 2H), 7.27 (m, 4H), 6.97 (m, 1H), 6.75 (m, 1H), 5.25 (t,

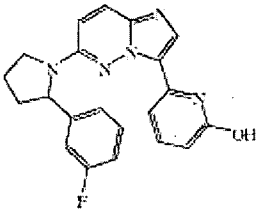
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1H), 4.28 (m, 4H), 4.14 (m, 3H), 3.93 (m, 2H), 3.73 (m, 1H), 2.83 (m, 1H), 1.92 (m, 2H), 1.82 (m, 1H), 1.41 (m, 1H). MS (m/z): 487.5
143		^{1}H RMN metanol-d4, d (ppm) 8.45 (s, 1H), 8.17 (d, 1H), 7.79 (d, 1H), 7.67 (m, 2H), 7.36 (m, 1H), 7.26 (m, 2H), 7.13 (d, 1H), 6.98 (m, 2), 5.40 (m, 1H), 4.63 (m, 2H), 4.34 (m, 1H), 4.15 (m, 3H), 3.88 (m, 1H), 3.79 (m, 1H), 3.06 (td, 2H), 2.31 (s, 3H), 2.12 (m, 2H), 1.85 (m, 2H). MS (m/z): 539.6

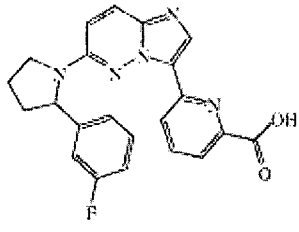
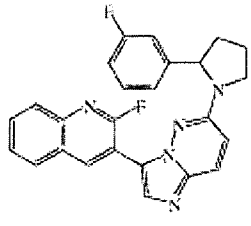
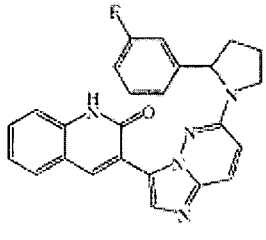
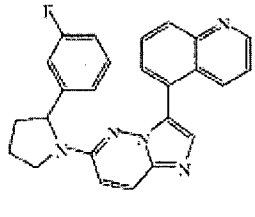
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
144		MS (m/z): 519.5
145		MS (m/z): 534.7
146		^{1}H RMN metanol-d4, d (ppm) 8.52 (s,1H), 8.15 (d, 1H), 7.81 (m, 3H), 7.36 (m, 1H), 7.25 (m, 2H), 7.00 (m, 2H), 5.40 (m, 1H), 4.34 (dd, 1H), 4.15 (m, 4H), 3.89 (td, 2H), 3.74 (m, 5H), 3.51 (m, 4H), 3.33 (m, 2H), 3.13 (s, 3H). MS (m/z): 566.7

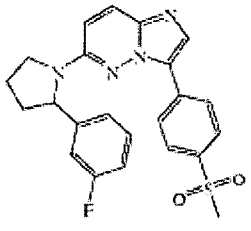
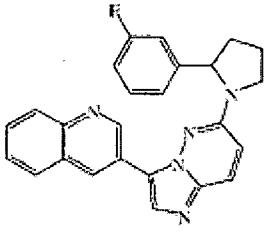
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
147		^{1}H RMN metanol-d4, d (ppm) 8.33 (s, 1H), 8.27 (s, 1H), 8.03 (d, 1H), 7.65 (d, 1H), 7.54 (m, 2H), 7.25 (m, 1H), 7.15 (m, 2H), 6.87 (m, 2H), 5.29 (m, 1H), 4.45 (m, 2H), 4.24 (dd, 1H), 4.04 (m, 3H), 3.77 (td, 1H), 3.66 (m, 1H), 3.20 (m, 1H), 3.00 (m, 2H), 1.99 (m, 2H), 1.75 (m, 2H). MS (m/z): 526.6
148		^{1}H RMN metanol-d4, d (ppm) 8.50 (s, 1H), 8.31 (s, 1H), 8.00 (d, 1H), 7.61 (d, 1H), 7.54 (m, 2H), 7.25 (m, 1H), 7.15 (m, 2H), 6.84 (m, 2H), 5.28 (m, 1H), 4.36 (m, 2H),

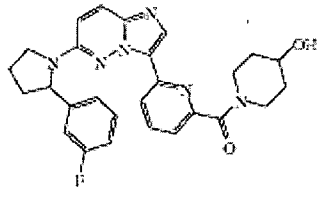
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		4.21 (dd, 1H), 4.04 (m, 3H), 3.77 (td, 1H), 3.66 (m, 1H), 3.03 (m, 3H), 2.08 (m, 2H), 1.81 (m, 2H). MS (m/z): 527.6
149		^{1}H RMN (400 MHz, D6 acetona) ppm: 8.40 (br, s, 1H), 8.35 (d, J = 8.1 Hz, 1H), 7.85 (d, J = 7.0 Hz, 1H), 7.62 (d, J = 6.2 Hz, 1H), 7.52-7.40 (m, 1H), 7.38-7.28 (m, 1H), 7.14 (d, J= 6.0 Hz, 1H), 7.04 (app d, J = 8.0 Hz, 1H), 6.85 (app dt, J = 8.4 Hz, 1H), 5.58 (d, J = 6.7 Hz, 1H), 4.31 app dt, J = 6.8, 2.5 Hz, 2H), 4.22-4.04 (m, 2H), 3.52-3.48 (m,

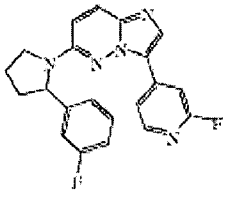
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1H), 3.28-3.07 (m, 3H), 2.39-2.31 (m, 1H), 2.22-2.10 (m, 1H), 1.97-1.77 (m, 4H), 1.67-1.42 (m, 4H). MS (m/z): 473.6
150		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.45 (br s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 7.4 Hz, 1H), 7.81-7.77 (m, 2H), 7.42-7.36 (m, 2H), 7.14 (app d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 6.81 (app t, J = 7.2 Hz, 1H), 6.18 (br s, 2H), 5.21 (d, J = 7.7 Hz, 1H), 3.95 (app q, J = 5.5 Hz, 1H), 3.67 (app q, J = 7.5 Hz, 1H), 2.62-2.45 (m,

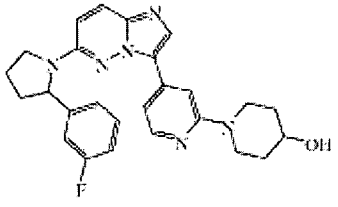
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2H), 2.22-2.02 (m, 1H), 1.95 (app t, J = 2.5 Hz, 1H). MS (m/z): 403.4
151		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.15 (br s, 1H), 7.90-7.83 (m, 1H), 7.58-7.52 (m, 1H), 7.34 (app q, J = 8.0 Hz, 1H), 7.10 (d, J = 7.2 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.89 (app t, J = 6.2 Hz, 2H), 6.82 (br s, 1H), 6.52 (app d, J = 4.6 Hz, 1.0H), 5.19 (d, J = 7.7 Hz, 1H), 4.05 (app q, J = 6.2 Hz, 1H), 3.74 (app q, J = 8.5 Hz, 1H), 2.64-2.40 (m, 2H), 2.20-2.00 (m, 1H), 1.95 (app t, J = 2.5 Hz,

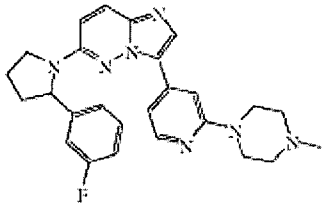
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1H). MS (m/z): 376.4
152		MS (m/z): 404.4
153		MS (m/z): 428.4
154		MS (m/z): 426.5
155		MS (m/z): 410.5

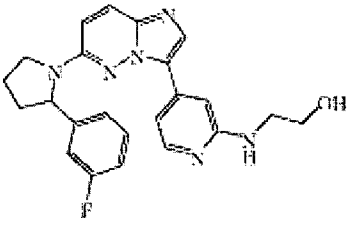
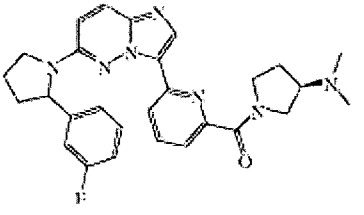
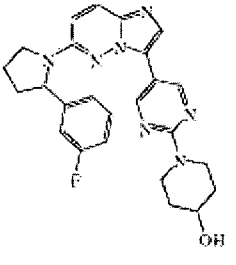
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
156		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.05-7.98 (m, 2H), 7.83 (app d, J = 6.8 Hz, 2H), 7.28 (app q, J = 6.2 Hz, 2H), 7.14 (br s, 1H), 6.98 (d, J = 7.0 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 6.85 (app t, J = 6.2 Hz, 2H), 5.02 (dd, J = 7.4, 2.2 Hz, 1H), 3.87 (app q, J = 5.5 Hz, 1H), 3.61 (app q, J = 8.5 Hz, 1H), 2.99 (s, 3H), 2.44-2.38 (m, 2H), 2.06-1.95 (m, 2H). MS (m/z): 437.5
157		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.14 (app t, J = 5.6 Hz, 2H), 8.12 (br s, 1H), 8.02 (br

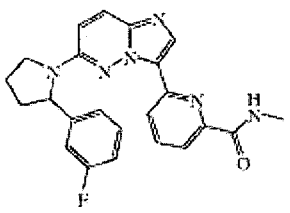
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		s, 1H), 7.98 (app dt, J = 6.8, 1.2 Hz, 2H), 7.78 (app dt, J = 6.8, 1.2 Hz, 2H), 7.30-7.25 (m, 2H), 7.15 (app d, J = 6.1 Hz, 1H), 7.04 (dd, J = 8.2, 1.9 Hz, 1H), 6.96 (t, J = 7.0 Hz, 1H), 5.22 (d, J = 7.94 Hz, 1H), 4.05 (m, 1H), 2.57-2.54 (m, 1H), 2.14-1.99 (m, 3H). MS (m/z): 410.5
158		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.30 (br s, 1H), 8.14 (app d, J = 2.6 Hz, 2H), 7.89 (br s, 1H), 7.54 (d, J = 6.8 Hz, 1H), 7.35 (q, J = 7.2 Hz, 1H), 7.25 (br s, 1H), 7.16 (d, J = 6.9 Hz, 1H), 7.08

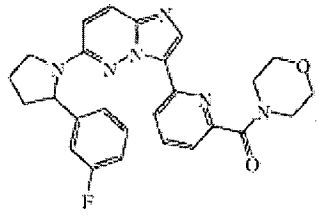
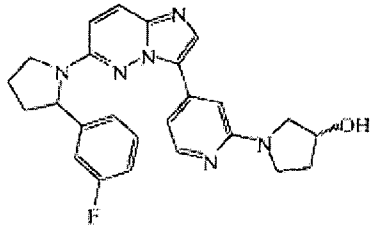
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(d, J = 8.2 Hz, 1H, 6.96 (t, J = 7.4 Hz, 1H), 5.23 (dd, J = 7.94, 1.9 Hz, 1H), 4.15 (br d, J = 7.8 Hz, 1H), 4.05 (app q, J = 6.8 Hz, 1H), 3.87 (app q, J = 6.7 Hz, 1H), 3.72 (q, J = 7.5 Hz, 1H), 3.67-3.63 (m, 1H), 3.33-3.12 (m, 4H), 2.57-2.54 (m, 1H), 2.14-1.99 (m, 2H), 1.65-1.59 (m, 2H). MS (m/z): 487.5
159		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.28 (d, J = 6.2 Hz, 1H), 8.20 (br s, 1H), 8.04 (app d, J = 6.6 Hz, 1H), 7.74 (s, 1H), 7.67 (s, 1H), 7.34 (q, J= 6.8 Hz, 1H), 7.22-7.14

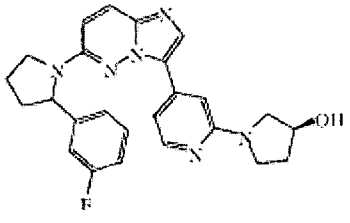
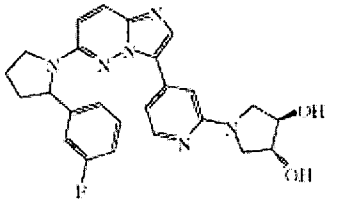
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(m, 2H), 7.03 (dd, J = 6.9, 1.2 Hz, 1H), 6.97 (dt, J = 6.4, 1.2 Hz, 1H), 5.18 (dd, J = 6.7, 1.9 Hz, 1H), 4.00 (app q, J = 5.8 Hz, 1H), 3.72 (app q, J = 6.4 Hz, 1H), 2.54-2.47 (m, 1H), 2.13-2.03 (m, 2H), 1.97-1.87 (m, 1H). MS (m/z): 378.4
160		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.18 (s, 1H), 8.04 (d, J = 6.9 Hz, 1H), 7.78 (s, 1H), 7.38 (q, J = 7.2 Hz, 1H), 7.28-7.19 (m, 1H), 7.10 (dd, J = 6.2, 1.2 Hz, 1H), 6.94 (app d, J = 6.8 Hz, 2H), 6.82-6.74 (m, 2H), 5.32 (app t, J = 2.9 Hz, 1H), 5.12 (dd, J =

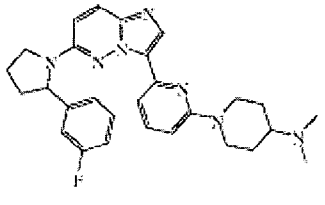
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		7.4, 1.6 Hz, 1H), 4.01-3.86 (m, 4H), 3.74 (app q, J = 6.8 Hz, 1H), 3.52 (app t, J = 6.0 Hz, 1H), 2.58-2.50 (m, 1H), 2.20-2.18 (m, 1H), 2.15-1.98 (m, 6H), 1.67-1.61 (m, 1H). MS (m/z): 459.5
161		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.08 (d, J = 7.1 Hz, 1H), 7.92 (s, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.62 (s, 1H), 7.41 (q, J = 8.2 Hz, 1H), 7.8 (app t, J = 8.9 Hz, 2H), 7.08 (d, J = 6.8 Hz, 1H), 6.95 (t, J = 5.8 Hz, 1H), 6.68 (dd, J = 7.4, 1.8 Hz, 1H), 5.17 (d, J =6.9 Hz, 1H), 3.98 (dd, J = 7.6, 2.6 Hz,

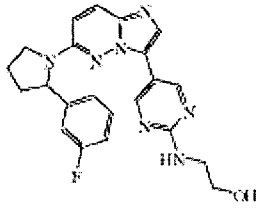
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1H), 3.72 (app q, J = 7.8 Hz, 1H), 3.58-3.51 (m, 4H), 2.46-2.40 (m, 4H), 2.20 (s, 3H), 2.08-2.03 (m, 1H). MS (m/z): 458.5
162		MS (m/z): 419.5
163		MS (m/z): 500.6
164		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.82 (s, 1H), 7.73 (s, 1H), 7.72-7.70 (m, 2H), 7.35 (q, J = 6.9 Hz, 1H), 7.09 (d, J = 6.9 Hz, 1H), 7.02 (d, J =

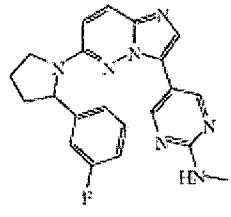
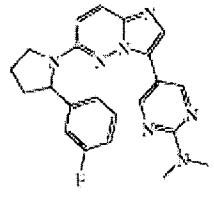
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		5.6 Hz, 1H), 6.89 (t, J = 5.8 Hz, 1H), 6.69 (dd, J = 6.9, 1.3 Hz, 1H), 5.07 (d, J = 7.9 Hz, 1H), 4.48-4.42 (m, 2H), 3.92-3.89 (m, 1H), 3.85-3.80 (m, 1H), 3.66 (q, J = 7.1 Hz, 1H), 3.38-3.32 (m, 2H), 2.48-2.42 (m, 1H), 2.13-2.03 (m, 4H), 1.50-1.45 (m, 2H). MS (m/z): 460.5
165		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.58 (s, 1H), 8.30-8.16 (m, 2H), 8.08 (app d, J = 6.9 Hz, 1H), 7.91 (br s, 1H), 7.42 (q, J = 5.9 Hz, 1H), 7.22 (br s 1H), 7.19 (dd, J = 6.9, 1.2 Hz, 1H), 7.02 (d,

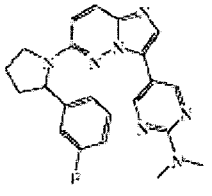
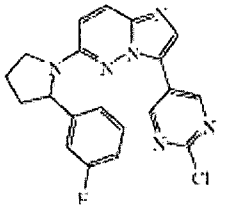
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		J = 7.2 Hz, 1H), 6.99 (dt, J = 6.8, 1.0 Hz, 1H), 5.24 (dd, J = 6.8, 1.9 Hz, 1H), 4.04 (app q, J = 6.4 Hz, 1H), 3.72 (app q, J = 5.4 Hz, 1H), 2.92 (d, J = 4.2 Hz, 3H), 2.54-2.47 (m, 1H), 2.19-2.10 (m, 2H), 2.03-1.95 (m, 1H). MS (m/z): 417.5
166		MS (m/z): 473.5
167		^{1}H RMN (600 MHz, D3 acetonitrilo) ppm: 8.08 (s, 1H), 8.04 (s, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.52-7.45 (m, 2H), 7.41 (app d, J = 3.2 Hz, 1H), 7.18 (br s,

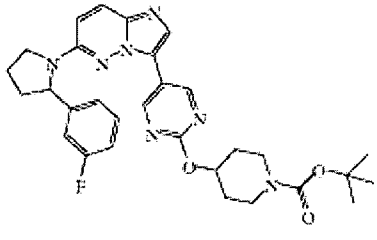
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2H), 7.01 (t, J = 6.1 Hz, 1H), 6.72 (d, J = 5.8 Hz, 1H), 5.27 (d, J = 6.9 Hz, 1H), 4.58 (br s, 1H), 4.11 (app t, J = 6.8 Hz, 1H), 4.04 (d, J = 4.5 Hz, 1H), 3.82 (q, J = 4.9 Hz, 1H), 3.77-3.54 (m, 3H), 3.52-3.48 (m, 1H), 2.66-2.60 (m, 1H), 2.20-2.01 (m, 4H). MS (m/z): 445.5
168		MS (m/z): 445.5
169		^{1}H RMN (600 MHz, D3 acetonitrilo) ppm: 8.06 (br s, 2H), 7.74 (d, J = 7.2 Hz, 1H), 7.48-7.42 (m,

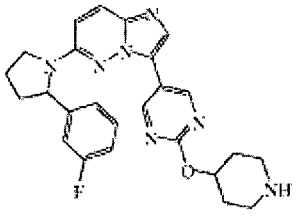
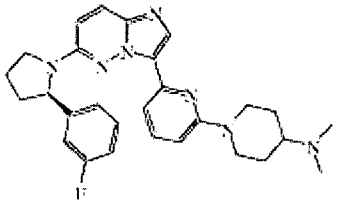
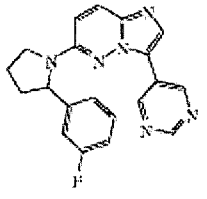
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2H), 7.28 (d, J = 7.2 Hz, 1H), 7.18 (br s, 2H), 7.01 (t, J = 6.8 Hz, 1), 6.72 (d, J = 6.8 Hz, 1H), 5.23 (d, J = 6.4 Hz, 1H), 4.58 (br s, 1H), 4.31 (br s, 2H), 4.11 (app t, J = 6.8 Hz, 1H), 3.88 (d, J = 4.5 Hz, 1H), 3.82 (t, J = 5.9 Hz, 1H), 3.61-3.59 (m, 2H), 3.21 (app d, J = 5.5 Hz, 1H), 2.63-2.58 (m, 1H), 2.16-2.00 (m, 4H). MS (m/z): 461.5
170		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.26 (s, 1H), 8.04 (br d, J = 6.2 Hz, 1H), 7.48 (br s, 1H), 7.39 (q, J = 7.5 Hz, 1H), 7.20 (s, 1H), 7.10-7.04

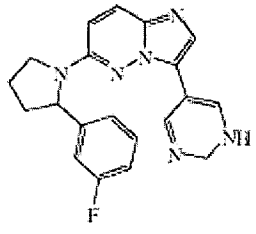
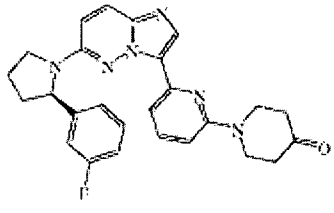
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(m, 2H), 7.03 (d, J = 7.0 Hz, 1H), 6.99 (dt, J = 6.9, 1.2 Hz, 1H), 6.82 (d, J = 6.8 Hz, 1H), 5.13 (dd, J = 6.4, 1.2 Hz, 1H), 4.58 (br s, 2H), 4.02-4.00 (m, 1), 3.62 (app q, J = 6.9 Hz, 1H), 3.22 (app t, 1H), 2.82 (app t, J = 6.5 Hz, 1H), 2.75 (br s, 6H), 2.62-2.52 (m, 2H), 2.48-2.38 (m, 3H), 2.11-2.00 (m, 3H), 1.84-1.80 (m, 1H). MS (m/z): 486.6
171		MS (m/z): 420.5

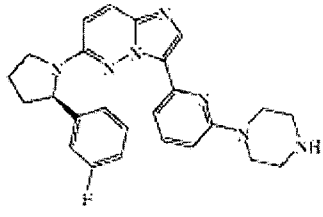
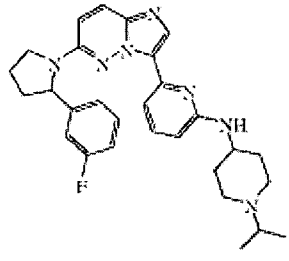
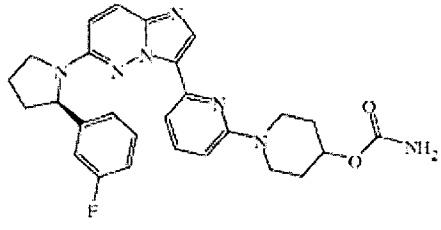
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
172		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.82 (s, 2H), 8.33 (d, 7.8 Hz, 1H), 8.18 (br s, 1H), 7.43-7.32 (m, 2H), 7.15 (d, J = 6.9 Hz, 1H), 7.04 (dd, J = 6.9, 1.5 Hz, 1H), 6.92 (t, J = 7.0 Hz, 1H), 5.27 (dd, J = 7.4, 2.2 Hz, 1H), 4.28-4.22 (m, 1H), 3.89 (app q, J = 6.7 Hz, 1H), 3.05 (s, 3H), 2.71-2.62 (m, 1H), 2.23-2.03 (m, 2H), 2.01-1.99 (m, 1H). MS (m/z): 390.4
173		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.62 (s, 2H), 8.06 (d, 7.9 Hz, 1H), 7.94 (br s, 1H), 7.23 (q, J = 6.4 Hz, 1H), 7.04 (app

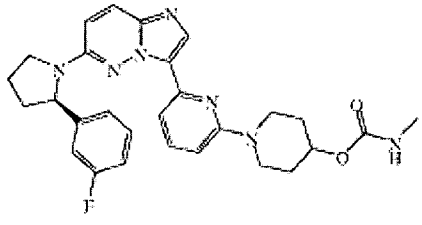
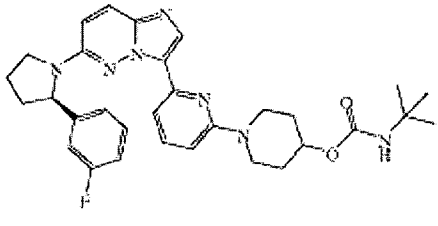
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		t, J = 6.5 Hz, 1H), 6.94 (d, J = 7.2 Hz, 1H), 6.82 (t, J = 6.1 Hz, 1H), 5.21 (dd, J = 7.0, 2.2 Hz, 1H), 3.92 (ddd, J = 6.6 Hz, 4.3 Hz, 1.9 Hz, 1H), 3.71-3.65 (m, 1H), 3.10 (s, 6H), 2.51-2.43 (m, 1H), 2.23-2.03 (m, 2H), 2.01-1.99 (m, 1H). MS (m/z): 404.5
174		MS (m/z): 486.6
175		MS (m/z): 395.8

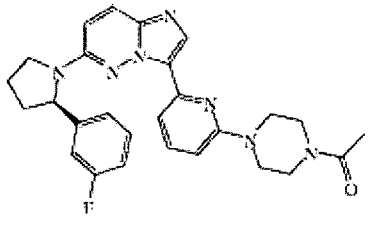
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
176		^{1}H RMN (400 MHz, D6 acetona) ppm: 8.91 (s, 2H), 7.80 (s, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.22 (q, J = 6.8 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 7.4 Hz, 1H), 6.82 (t, J = 7.1 Hz, 1H), 6.67 (d, J = 7.2 Hz, 1H), 5.11 (t, J = 5.4 Hz, 1H), 5.02 (dd, J = 7.0, 2.2 Hz, 1H), 3.96-3.87 (m, 1H), 3.74-3.63 (m, 2H), 3.01 (app q, J = 5.2 Hz, 1H), 2.72 (s, 9H), 2.43-2.38 (m, 1H), 2.13-1.99 (m, 4H), 1.67-1.58 (m, 3H), 1.54-1.48 (m, 2). MS (m/z): 560.6

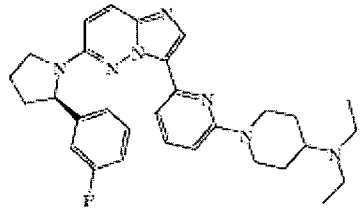
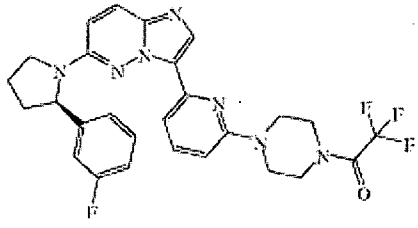
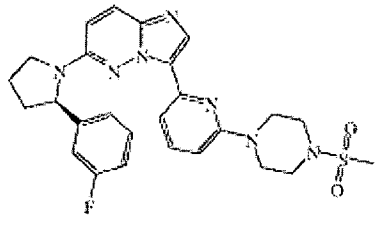
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
177		MS (m/z): 460.5
178		MS (m/z): 486.6
179		^{1}H RMN (400 MHz, D6 DMSO) ppm: 9.30 (s, 2H), 9.06 (s, 1H), 8.20 (s, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.35 (q, J = 6.4 Hz, 1H), 7.15-5.05 (m, 2H), 7.03 (app t, J = 6.9 Hz, 1H), 6.88 (d, J = 7.2 Hz, 1H), 5.19 (dd, J = 7.0, 2.2 Hz, 1H), 3.99 (app d, J = 6.9 Hz, 1H), 3.66 (m, 1H), 3.10 (s, 6H), 2.51-2.43 (m, 1H), 2.23-2.03 (m,

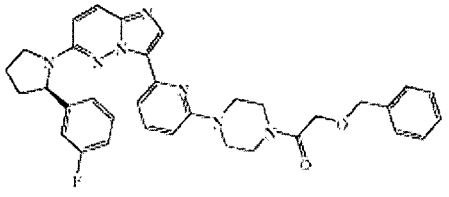
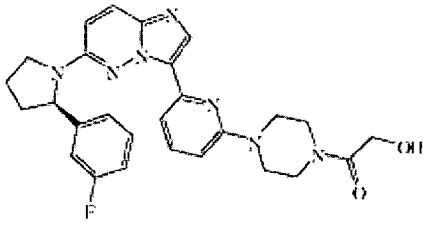
# Comp.	Estructura	Datos Físicos ¹H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2H), 2.01-1.99 (m, 1H). MS (m/z): 361.4
180		MS (m/z): 363.4
181		¹H RMN (400 MHz, D6 acetona) ppm: 8.45 (s, 1H), 8.28 (d, J = 6.7 Hz, 1H), 7.64-7.58 (m, 2H), 7.38 (app q, J = 6.9 Hz, 1H), 7.29 (br s, 1H), 7.21 (d, J = 7.3 Hz, 1H), 7.19 (d, J = 6.9 Hz, 1H), 7.02-6.97 (m, 2H), 5.34 (dd, J = 6.8, 2.48 Hz, 1H), 4.22-4.17 (m, 1H), 4.08 (app t, J = 8.4 Hz, 4H), 3.82 (app q, J = 6.4 Hz, 1H), 2.62-2.57 (m, 1H), 2.48 (app t,

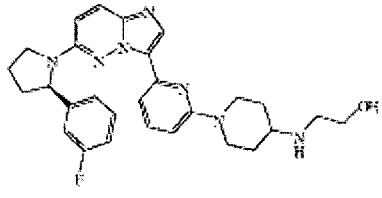
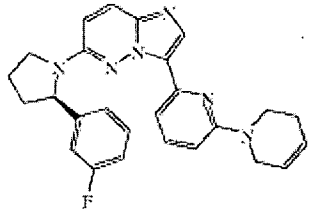
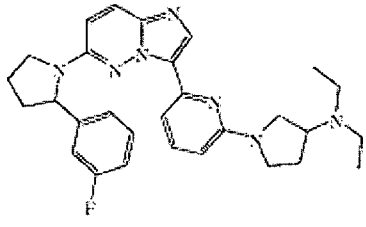
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		J = 8.4 Hz, 4H), 2.21-2.10 (m, 2H), 2.03-1.99 (m, 1H). MS (m/z): 457.5
182		MS (m/z): 444.5
183		MS (m/z): 500.6
184		^{1}H RMN (400 MHz, D6 acetona) ppm: 8.51 (s, 1H), 8.38 (d, J = 6.4 Hz, 1H), 7.54 (br s, 1H), 7.42 (app q, J = 6.3 Hz, 1H), 7.28 (d, J= 6.9 Hz, 1H), 7.02 (dt, J = 6.7, 1.6 Hz, 1H), 6.92 (d, J = 6.9 Hz,

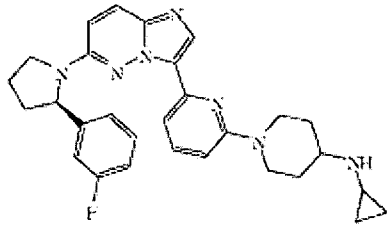
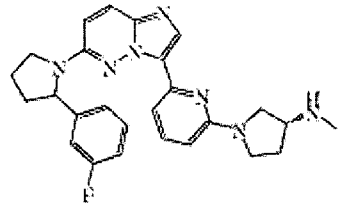
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1H), 5.82 (br s, 2H), 5.37 (dd, J = 6.0, 1.5 Hz, 1H), 4.88-4.77 (m, 1H), 4.32-4.26 (m, 2H), 3.92 (app q, J = 7.4 Hz, 4H), 3.42 (app dt, J = 6.8, 1.9 Hz, 1H), 2.68-2.63 (m, 1H), 2.38-2.22 (m, 2H), 2.06-2.02 (m, 1H), 2.00-1.97 (m, 1H), 1.64-1.55 (m, 2H). MS (m/z): 502.6
185		MS (m/z): 516.6
186		MS (m/z): 558.7

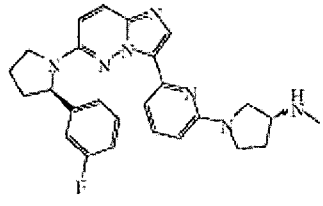
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
187		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.28 (s, 1H), 8.08 (s, 1H), 7.54 (br s, 1H), 7.38 (app q, J = 6.8 Hz, 1), 7.35-7.26 (m, 2H), 7.18 (d, J= 6.9 Hz, 1H), 7.10 (d, J = 6.9 Hz, 1H), 7.00 (dt, J = 7.2, 1.9 Hz, 1H), 6.82 (d, J = 6.9 Hz, 1H), 5.22 (dd, J = 6.4, 1.7 Hz, 1H), 4.08-4.02 (m, 1H), 3.76 (app q, J = 7.0 Hz, 1H), 3.68-3.62 (m, 4H), 3.59-3.54 (m, 4H), 2.60-2.48 (m, 1H), 2.38-2.22 (m, 2H), 2.14-2.02 (m, 1H), 1.97 (s, 3H). MS (m/z): 486.6

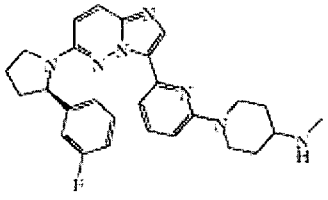
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
188		MS (m/z): 514.7
189		MS (m/z): 540.5
190		^{1}H RMN (400 MHz, D6 DMSO) ppm: 8.38 (s, 1H), 8.04 (d, J = 7.5 Hz, 1H), 7.56 (br s, 1H), 7.39 (app q, J = 7.2 Hz, 1H), 7.23 (d, J = 7.7 Hz, 1H), 7.17-7.11 (m, 2H), 7.05 (t, J = 7.9 Hz, 1H), 6.98 (d, J = 7.9 Hz, 1H), 6.90 (br d, J = 8.2 Hz, 1H), 5.22 (dd, J = 7.4, 2.2 Hz, 1H), 4.03-4.01 (m, 1H), 3.71 (br s, 2H), 3.21 (app t, J = 5.6

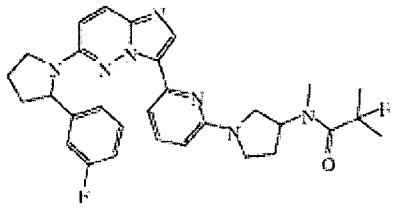
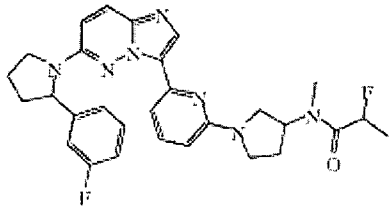
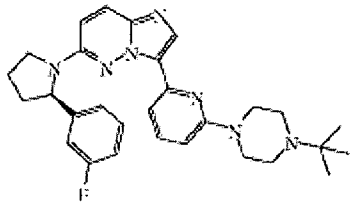
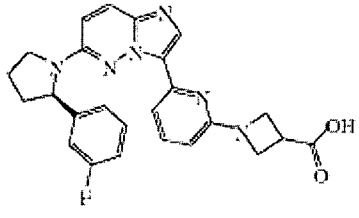
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		Hz, 1H), 2.90 (s, 3H), 2.56-2.42 (s, 6H), 2.28-2.12 (m, 2H), 2.04-1.90 (m, 2H). MS (m/z): 522.6
191		MS (m/z): 592.7
192		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.12 (s, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.60 (br s, 1H), 7.49 (t, J = 7.0 Hz, 1H), 7.36 (app q, J = 7.4 Hz, 1H), 7.18 (d, J = 7.2 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 6.98 (t, J = 7.7 Hz, 1H), 6.76 (dt, J = 7.2, 1.1 Hz, 1H), 6.67 (d, J = 6.9 Hz, 1H), 5.16 (dd, J = 7.8, 2.2

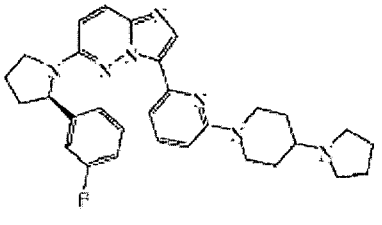
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		Hz, 1H), 4.18 (br s, 2H), 3.93 (p, J = 3.8 Hz, 1H), 3.67-3.57 (m, 8H), 3.42-3.38 (m, 1H), 2.52-2.45 (m, 1H), 2.18-2.06 (m, 2H), 1.92-1.88 (m, 1H). MS (m/z): 502.6
193		MS (m/z): 502.6
194		MS (m/z): 441.5
195		^{1}H RMN (400 MHz, D6 acetona) ppm: 8.32 (s, 1H), 8.14 (d, J = 7.6 Hz, 1H), 7.55-7.46 (m, 1H), 7.41 (app q, J = 7.4 Hz, 1H), 7.41 (app q, J = 5.4

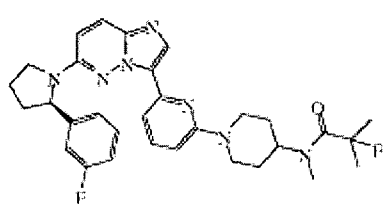
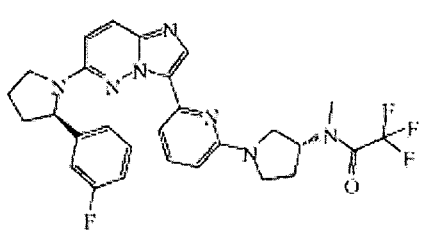
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		Hz, 1H), 7.21-7.11 (m, 2H), 7.03 (d, J = 7.6 Hz, 1H), 6.88 (t, J = 7.7 Hz, 1H), 6.42 (d, J = 7.2 Hz, 1H), 5.18 (d, J = 5.6 Hz, 1H), 4.10-4.00 (m, 2H), 3.70-3.59 (m, 3H), 3.38-3.04 (m, 8H), 2.50-2.40 (m, 2H), 2.06-1.99 (m, 2H), 2.18-2.06 (m, 2H), 1.42 (t, J = 6.0 Hz, 4H). MS (m/z): 500.6
196		MS (m/z): 498.6
197		MS (m/z): 458.5

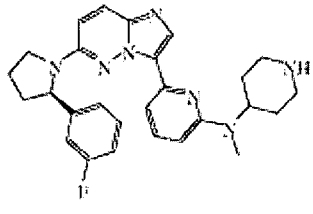
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
198		^{1}H RMN (400 MHz, D6 acetona) ppm: 8.28 (d, J = 7.1 Hz, 1H), 8.04 (s, 1H), 7.42 (app q, J = 7.8 Hz, 1H), 7.38 (br s, 1H), 7.28 (d, J = 7.4 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.94 (t, J = 7.7 Hz, 1H), 6.42 (d, J = 6.4 Hz, 1H), 5.28 (d, J = 6.6 Hz, 1H), 4.18-4.04 (m, 2H), 3.98 (app d, J = 6.8 Hz, 1H), 3.88-3.62 (m, 4H), 3.48-3.42 (m, 1H), 2.92 (s, 3H), 2.77-2.70 (m, 1H), 2.67-2.56 (m, 1H), 2.32-2.26 (m, 2H), 2.18-2.09 (m, 1H). MS (m/z): 458.5

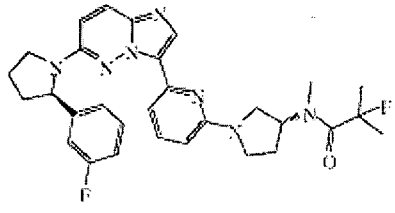
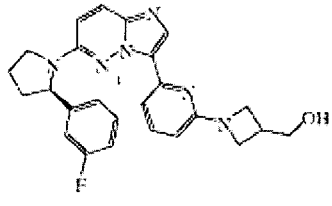
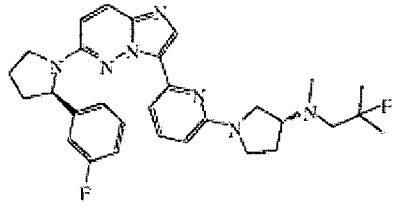
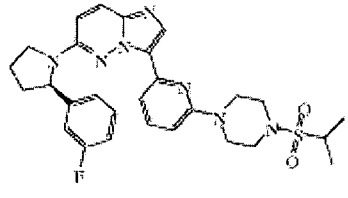
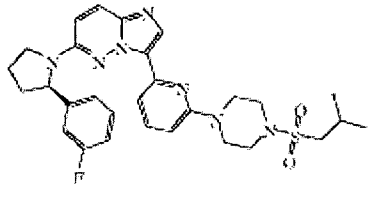
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
199		^{1}H RMN (400 MHz, D6 acetona) ppm: 9.43-9.02 (br s, 2H), 8.48 (br s, 1H), 8.35 (s, 1H), 8.56 (s, 1H), 7.42 (app q, J = 7.8 Hz, 1H), 7.31 (d, J = 5.6 Hz, 1H), 7.20 (d, J = 7.4 Hz, 1H), 7.02 (dt, J = 8.4, 1.9 Hz, 1H), 6.92 (br d, J = 4.5 Hz, 1H), 5.35 (d, J = 4.6 Hz, 1H), 4.20 (app d, J = 4.9 Hz, 1H), 3.98 (app t, J = 6.8 Hz, 1H), 3.58-3.52 (m, 1H), 3.08-2.98 (m, 3H), 2.82 (s, 3H), 2.71-2.60 (m, 1H), 2.38 (app d, J = 6.8 Hz, 2H), 2.27-2.18 (m, 2H), 2.32-2.26 (m, 2), 1.88-1.69 (m, 2H). MS (m/z): 472.6

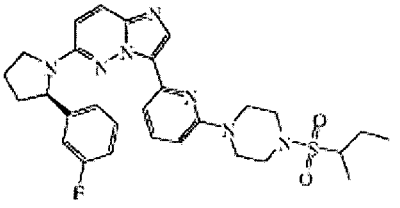
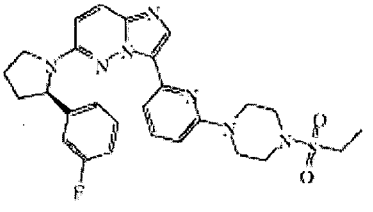
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
200		MS (m/z): 546.6
201		MS (m/z): 532.6
202		MS (m/z): 500.6
203		^{1}H RMN (400 MHz, D6 acetona) ppm: 8.28 (br s, 1H), 8.15 (d, J = 7.8 hz, 1H), 7.56 (br s, 2H), 7.46 (app q, J = 7.8 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.30 (br s, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.04 (dt, J = 7.4, 1.9 Hz, 1H), 6.42

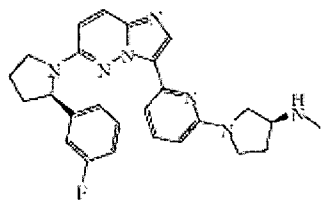
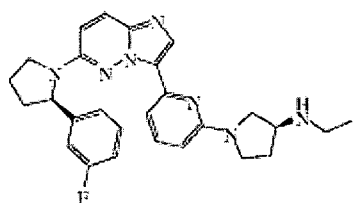
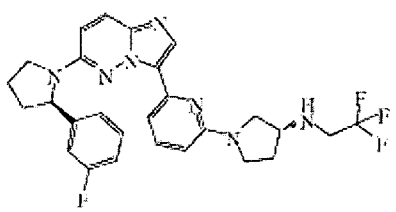
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(br d, J = 6.5 Hz, 1H), 5.25 (d, J = 6.6 Hz, 1H), 4.20 (app d, J = 5.9 Hz, 2H), 4.12-4.06 (m, 2H), 3.98 (p, J = 6.8 Hz, 1H), 3.52-3.48 (m, 1H), 2.77-2.68 (m, 1H), 2.28-2.18 (m, 2H), 2.02-1.97 (m, 1H). MS (m/z): 459.5
204		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.29 (br s, 1H), 8.19 (d, J = 6.7 Hz, 1H), 7.52 (br s, 2H), 7.38 (app q, J = 7.3 Hz, 1H), 7.24 (br s, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.08 (d, J = 7.9 Hz, 1H), 6.94 (dt, J = 7.6, 1.9 Hz, 1H), 6.82 (d, J = 5.5 Hz, 1H),

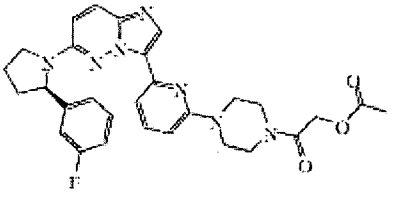
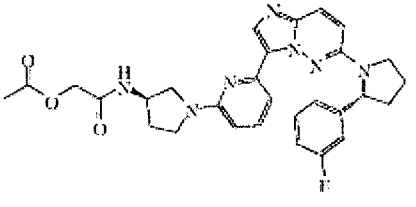
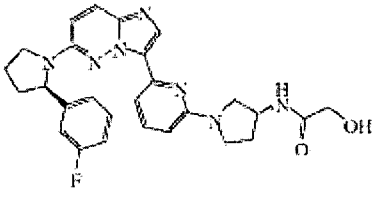
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		5.23 (d, J = 6.9 z, 1H), 4.52 (app br d, J = 7.9 Hz, 2H), 4.04-3.99 (m, 1H), 3.78 (q, J = 6.9 Hz, 1H), 3.69-3.62 (m, 1H), 3.33-3.21 (m, 2H), 3.09-3.02 (m, 1H), 2.83 (app t, J = 8.0 Hz, 2H), 2.77-2.50 (m, 6H), 2.28-2.08 (m, 4H), 1.84-1.74 (m, 2H). MS (m/z): 512.6
205		MS (m/z): 560.7
206		MS (m/z): 554.6

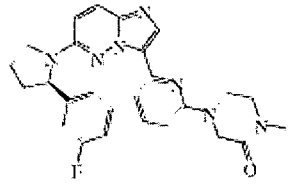
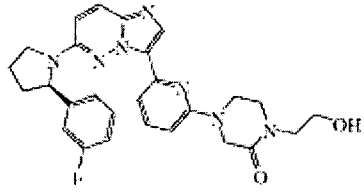
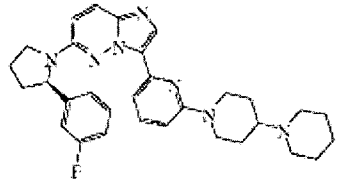
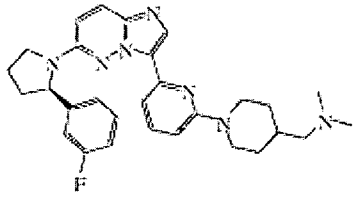
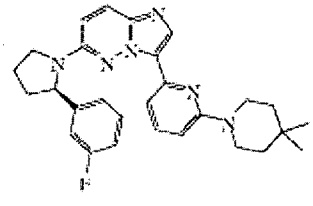
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
207		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.32 (br s, 1H), 8.21 (s, 1H), 8.02 (d, J = 7.4 Hz, 1H), 7.76 (br s, 1H), 7.38 (app t, J = 2.3 Hz, 1H), 7.26 (app q, J = 7.2 Hz, 1H), 7.04-6.97 (m, 2H), 6.92 (d, J = 7.6 Hz, 1H), 6.52 (d, J = 6.5 Hz, 1H), 5.15 (d, J = 6.6 Hz, 1H), 4.78 (dt, J = 6.9, 1.9 Hz, 1H), 3.91-3.79 (m, 1H), 3.58 (q, J = 6.8 Hz, 1H), 3.34 (app d, J = 8.2 Hz, 1H), 3.03 (br q, J = 4.5 Hz, 1H), 2.78 (s, 3H), 2.67-2.48 (m, 4H), 2.28-2.08 (m, 4H), 1.82-1.73 (m, 2H). MS (m/z): 472.6

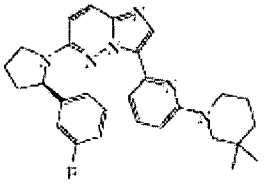
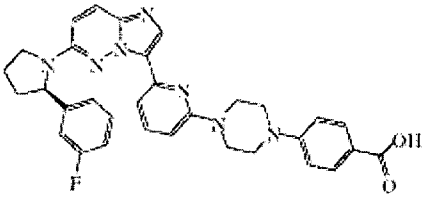
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
208		MS (m/z): 546.6
209		MS (m/z): 445.5
210		MS (m/z): 532.6
211		MS (m/z): 550.7
212		MS (m/z): 564.7

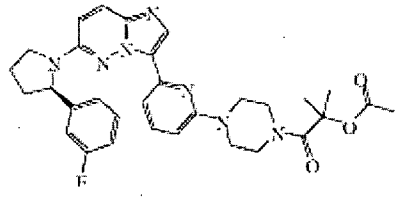
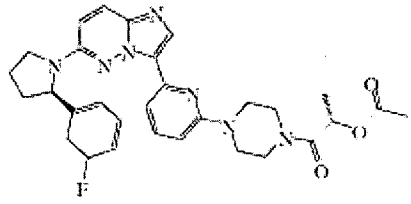
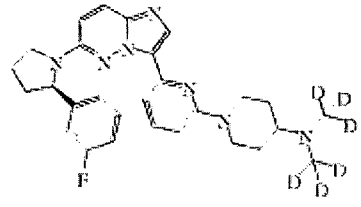
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
213		MS (m/z): 564.7
214		^{1}H RMN (400 MHz, D6 DMSO) ppm: 8.35 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.54 (br s, 2H), 7.39 (q, J = 7.0 Hz, 1H), 7.21-7.14 (m, 2H), 7.06 (d, J = 7.0 Hz, 1H), 7.00 (br s, 1H), 6.87 (d, J = 7.8 Hz, 1H), 5.20 (d, J = 6.8 Hz, 1H), 4.08-4.00 (m, 1H), 3.78-3.67 (m, 2H), 3.30-3.26 (m, 1H), 2.67 (q, J = 7.0 Hz, 2H), 2.62-2.54 (m, 6H), 2.42-2.35 (m, 1H), 2.08-2.00 (m, 2H), 1.92-1.88 (m, 1H), 1.25 (t, J = 7.4 Hz, 3H).

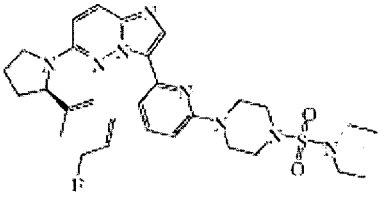
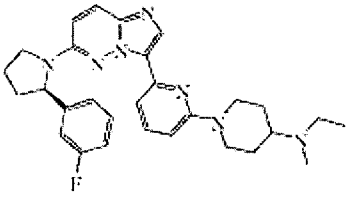
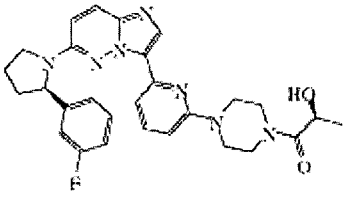
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		MS (m/z): 536.6
215		MS (m/z): 458.5
216		MS (m/z): 472.6
217		^{1}H RMN (400 MHz, D6 DMSO) ppm: 8.20 (br s, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.48 (br s, 1H), 7.38 (app q, J = 6.3 Hz, 1H), 7.38 (app q, J = 6.3 Hz, 1H), 7.22 (d, J = 7.2 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 7.04 (d, J = 6.7 Hz, 1H), 6.42 (d, J = 7.5 Hz, 1H), 5.25 (d, J = 6.1 Hz, 1H), 4.18-4.04 (m, 3H),

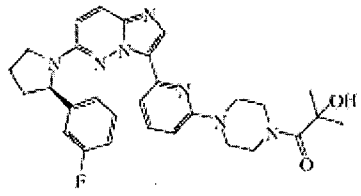
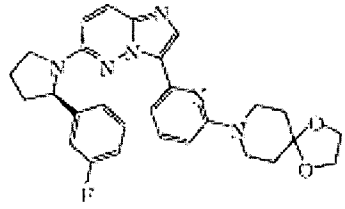
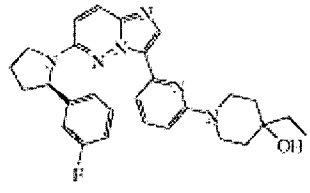
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		3.92 (dd, 10.1, 6.7 Hz, 1H), 3.78 (q, J = 6.8 Hz, 1H), 3.72 (q, J = 5.8 Hz, 1H), 3.48 (app d, J = 7.2 Hz, 1H), 2.92 (s, 2H), 2.72-2.64 (m, 1H), 2.58-2.53 (m, 2H), 2.21-2.17 (m, 2H), 2.05-1.98 (m, 1H). MS (m/z): 526.5
218		MS (m/z): 544.6
219		MS (m/z): 544.6
220		MS (m/z): 502.6

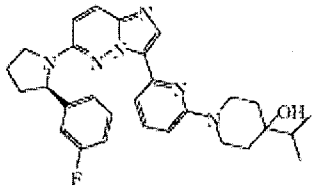
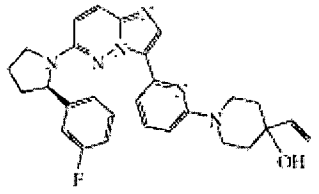
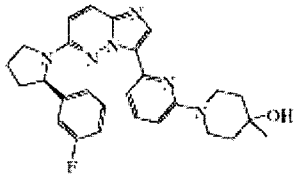
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
221		MS (m/z): 472.5
222		MS (m/z): 502.6
223		MS (m/z): 526.7
224		MS (m/z): 500.6
225		^{1}H RMN (400 MHz, D6 DMSO) ppm: 8.34 (s, 1H), 8.04 (br d, J = 6.4 Hz, 1H), 7.46 (br s, 2H), 7.38 (q, J = 7.6 Hz, 1H), 7.24 (s, 1H), 7.18 – 7.10 (m,

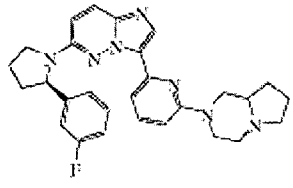
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2H), 7.05 (t, J = 6.7 Hz, 1H), 6.82 (d, J = 6.8 Hz, 1H), 5.21 (d, J = 6.5 Hz, 1H), 4.05 – 4.02 (m, 2H), 3.70 (q, J = 5.6 Hz, 1H), 3.56 (app q, J = 6.2 Hz, 1H), 2.82 – 2.71 (m, 2H), 2.54 – 2.44 (m, 1H), 2.08 – 2.04 (m, 2H), 1.90 – 1.82 (m, 1H), 1.38 – 1.35 (m, 4H), 0.95 (s, 6H). MS (m/z): 471.6
226		MS (m/z): 471.6
227		MS (m/z): 564.6

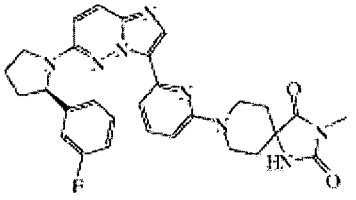
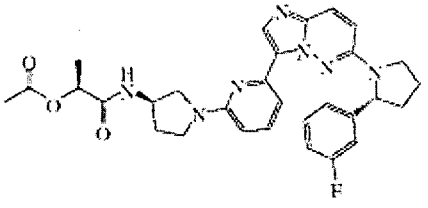
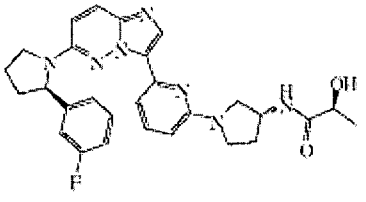
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
228		MS (m/z): 572.6
229		MS (m/z): 558.6
230		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.20 (s, 1H), 8.00 (br d, J = 6.4 Hz, 1H), 7.40 (br s, 2H), 7.30 (q, J = 7.6 Hz, 1H), 7.04 (d, J = 6.9 Hz, 1H), 6.95 (app d, J = 7.7 Hz, 2H), 6.92 (dt, J = 6.9, 1.2 Hz, 1H),6.62 (d, J = 6.2 Hz, 1H), 5.03 (dd, J = 6.5, 1.2 Hz, 1H), 4.45 – 4.40 (m, 2H), 3.98 – 3.90 (m, 1H), 3.62 (app q, J =

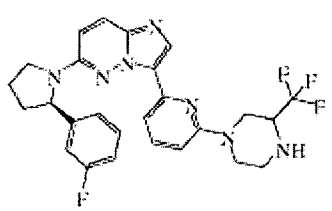
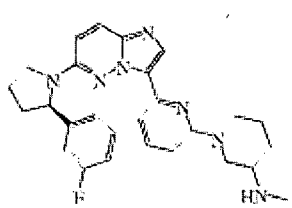
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		6.9 Hz, 1H), 3.62 (app q, J = 6.9 Hz, 1H), 3.22 (app t, 1H), 2.80 (app t, J = 6.0 Hz, 1H), 2.62 -2.52 (m, 2H), 2.48 – 2.38 (m, 3H), 2.05 – 1.99 (m, 3H), 1.69 – 1.67 (m, 1H). MS (m/z): 492.6
231		MS (m/z): 579.7
232		MS (m/z): 500.6
233		MS (m/z): 516.6

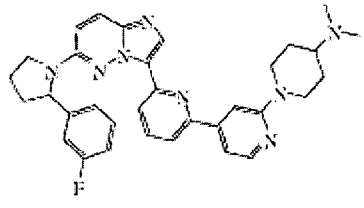
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
234		MS (m/z): 530.5
235		MS (m/z): 501.6
236		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.18 (s, 1H), 7.92 (br s, 2H), 7.38 (br s, 2H), 7.28 (app q, J = 7.0 Hz, 1H), 7.08 (s, 1H), 7.02 (d, J = 7.3 Hz, 1H), 6.83 (app t, J = 7.2 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 5.08.(d, J = 6.9 Hz, 1H), 3.95 – 3.81 (m, 3H), 3.62 (app q, J = 6.2 Hz, 1H), 3.22 (app t, J = 5.0 Hz, 2H), 2.55 - 2.43

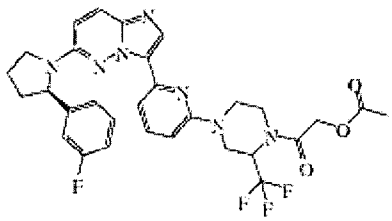
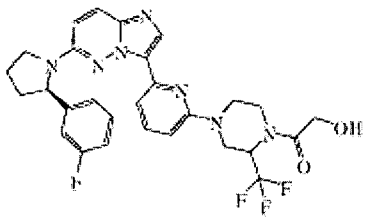
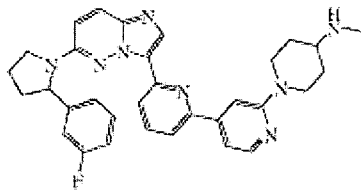
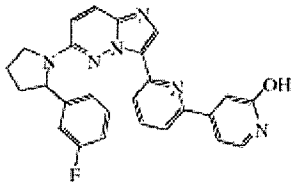
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(m, 1H), 2.09 – 1.99 (m, 2H), 1.88 – 1.80 (m, 1H), 1.67 (br s, 1H), 1.50 – 1.45 (m, 2H), 1.38 (q, J = 5.9 Hz, 2H), 0.80 (t, J = 5.0 Hz, 3H). MS (m/z): 487.6
237		MS (m/z): 501.6
238		MS (m/z): 485.6
239		MS (m/z): 473.6

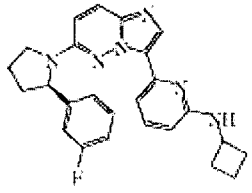
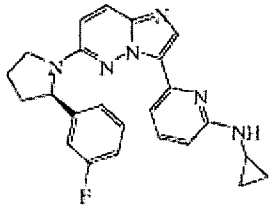
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
240		^{1}H RMN (400 MHz, D6 acetona) ppm: 8.51 (br s, 1H), 8.41 (d, J = 8.8 Hz, 1H), 7.68 – 7.52 (m, 2H), 7.48 (br s, 1H), 7.38 (app q, J = 7.5 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 6.94 (app dt, J = 7.8, 1.9 Hz, 1H), 6.90 (d, J = 5.6 Hz, 1H), 5.38 (d, J = 6.4 Hz, 1H), 5.05 (dd, J = 5.4 Hz, 1.7 Hz, 1H), 4.72 (app t, J = 7.2 Hz, 1H), 4.22 (d, J = 4.2 Hz, 2H), 4.18 (app q, J = 6.0 Hz, 1H), 4.05 (br s, 1H), 3.98 – 3.62 (m, 3H), 3.48 – 3.40 (m, 2H), 3.28 – 3.22 (m, 1H), 3.18 – 3.00 (m, 1H), 2.65 – 2.59 (m, 1H), 2.39 –

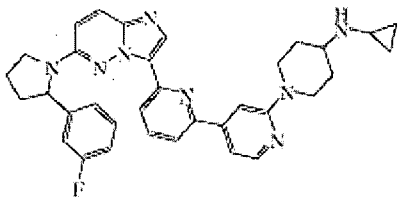
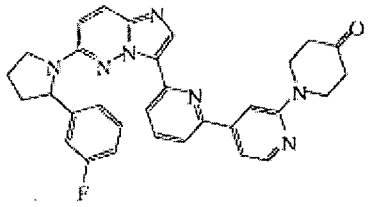
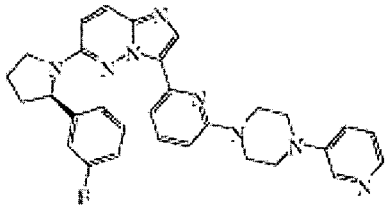
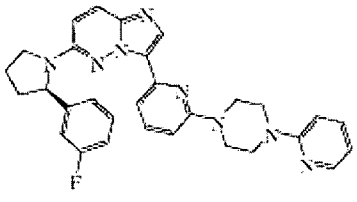
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1.99 (m, 5H). MS (m/z): 484.6
241		MS (m/z): 541.6
242		MS (m/z): 558.6
243		^{1}H RMN (400 MHz, D6 acetona) ppm: 8.21 (br s, 1H), 7.98 – 7.82 (m, 2H), 7.45 (app q, J = 6.5 Hz, 2H), 7.40 (app q, J = 6.2 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 6.94 (dt, J = 8.6, 1.9 Hz, 1H), 6.90 (br s, 1H), 6.42 (d, J = 6.2 Hz, 1H), 5.22 (d, J = 6.4 Hz, 1H), 4.54 (app p, J = 6.2

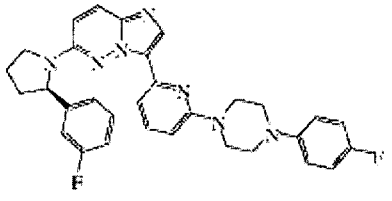
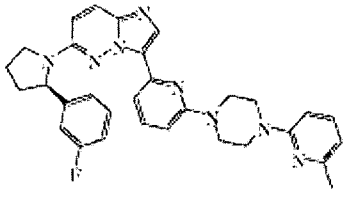
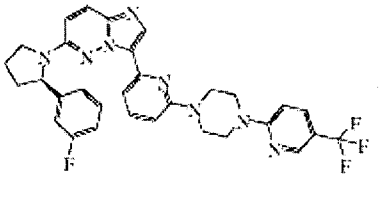
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		Hz, 2H), 4.22 (app q, J = 5.6 Hz 2H), 3.78 (q, J = 6.8 Hz, 1H), 3.68 – 3.62 (m, 1H), 3.58 – 3.53 (m, 1H), 3.42 (dd, J = 4.8, 1.6 Hz, 1H), 3.21 (app t, J = 7.2 Hz, 2H), 2.62 – 2.56 (m, 1H), 2.31 – 2.25 (m, 1H), 2.18 – 1.99 (m, 3H9, 1.42 (d, J = 5.4 Hz, 3H). MS (m/z): 516.6
244		MS (m/z): 512.5
245		MS (m/z): 472.6

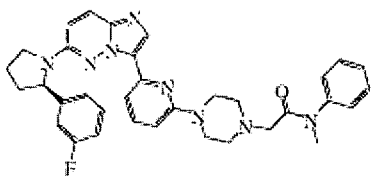
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
246		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.56 (br s, 1H), 8.24 (d, J = 7.2 Hz, 1H), 8.18 (app d, J = 6.5 Hz, 2H), 7.95 (d, J = 6.2 Hz, 1H), 7.88 (br s, 1H), 7.78 (s, 1H), 7.52 (d, J = 6.4 Hz, 1H), 7.38 (app q, J = 6.8 Hz, 1H), 7.28 (br s, 1H), 7.22 (d, J = 7.2 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 6.92 (dt, J = 8.6, 1,9 Hz, 1H), 5.22 (dd, J = 6.9, 1.9 Hz, 1H), 4.51 (app d, J = 10 Hz, 2H), 4.02 (app q, J = 3.6 Hz, 1H), 3.78(q, J = 6.8 Hz, 1H), 3.48 (t, J = 5.8 Hz, 1H), 3.21 (app t, J = 7.2 Hz, 2H), 2.82 (s, 6H), 2.37 – 2.25 (m, 2H), 2.18

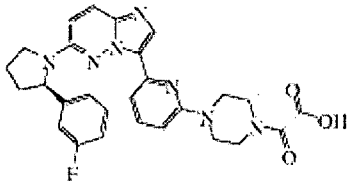
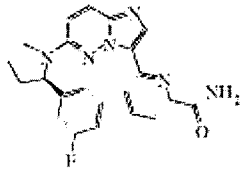
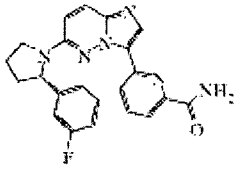
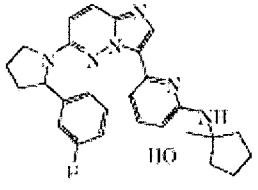
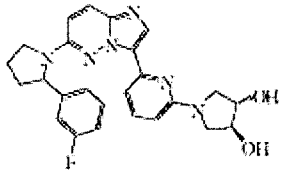
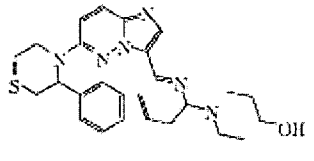
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		– 2.03 (m, 2H), 1.97 – 1.86 (m, 4H) MS (m/z): 563.7
247		MS (m/z): 612.6
248		MS (m/z): 570.6
249		MS (m/z): 549.7
250		MS (m/z): 453.5

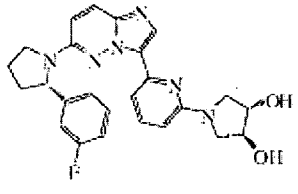
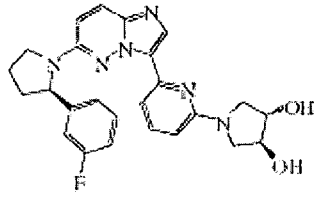
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
251		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.61 (br s, 1H), 8.14 (d, J = 7.7 Hz, 1H), 7.62 (br s, 1H), 7.58 (s, 1H), 7.42 (app q, J = 7.8 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.26 (d, J = 7.4 Hz, 1H), 7.17 (d, J = 7.2 Hz, 1H), 7.02 (t, J = 8.2 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 4.17 (app q, J = 6.6 Hz, 1H), 3.82 (q, J = 6.8 Hz, 1H), 2.77 – 2.67 (m, 1H), 2.48 – 2.35 (m, 2H), 2.38 – 2.06 (m, 5H), 1.97 – 1.82 (m, 2H) MS (m/z): 429.5
252		MS (m/z): 415.5

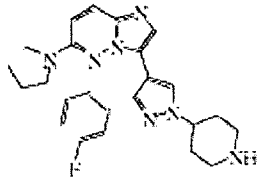
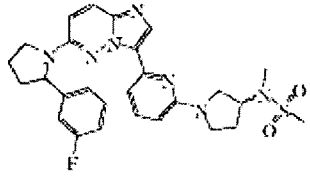
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
253		MS (m/z): 575.7
254		MS (m/z): 534.6
255		MS (m/z): 521.6
256		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.38 (br s, 2H), 7.58 (s, 1H), 7.42 (q, J = 7.7 Hz, 1H), 7.39 (d, J = 6.7 Hz, 1H), 7.39 – 7.31 (m, 4H), 7.28 (br s, 1H), 7.22 (d, J = 6.2 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.98 (t, J = 7.2

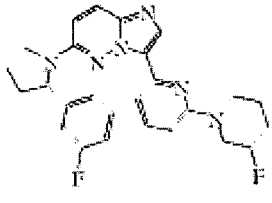
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		Hz, 1H), 6.88 (d, J = 7.2 Hz, 1H), 5.27 (d, J = 7.2 Hz, 1H), 4.22 – 4.15 (m, 1H), 4.12 – 4.00 (m, 4H), 3.82 (app q, J = 6.7 Hz, 1H), 3.71 – 3.59 (m, 4H), 2.67 – 2.59 (m, 1H), 2.28 – 2.19 (m, 2H), 2.08 – 2.00 (m, 1H). MS (m/z): 521.6
257		MS (m/z): 538.6
258		MS (m/z): 535.6
259		MS (m/z): 589.6

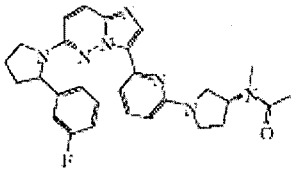
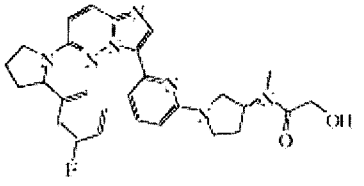
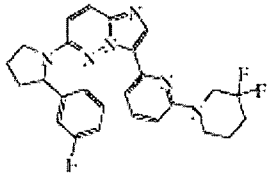
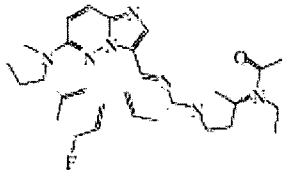
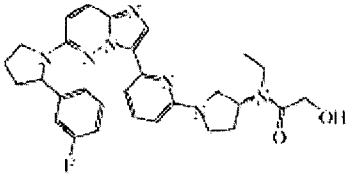
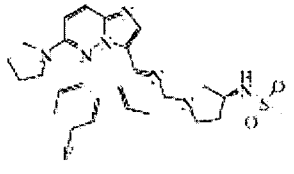
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
260		^{1}H RMN (400 MHz, D3 acetonitrilo) ppm: 8.35 (br s, 1H), 8.18 (app t, J = 4.5 Hz, 1H), 7.80 – 7.67 (m, 1H), 7.62 (app t, J = 6.7 Hz, 2H), 7.55 (q, J = 6.2 Hz, 1H), 7.35 (br s, 1H), 7,28 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.15 (app t, J 8.2 Hz, 2H), 7.08 (dt, J = 7.2, 1.9 Hz, 1H), 6.95 (d, J = 6.9 Hz, 1H), 6.85 – 6.78 (m, 1H), 5.37 (d, J = 6.2 Hz, 1H), 4.32 (br s, 2H), 4.25 – 4.11 (m, 4H), 3.82 (s, 3H), 3.62 – 3.43 (m, 4H), 2.62 – 2.64 (m, 1H), 2.25 – 2.14 (m, 2H), 2.08 – 2.00 (m, 1H). MS (m/z): 591.7

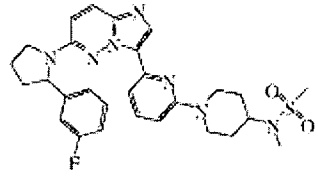
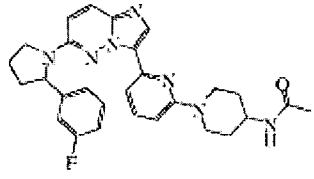
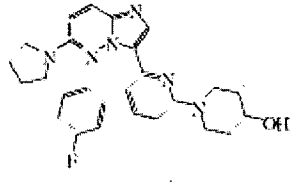
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
261		MS (m/z): 516.5
262		MS (m/z): 403.4
263		MS (m/z): 403.4
264		MS (m/z): 473.6
265		MS (m/z): 461.5
266		MS (m/z): 473.6

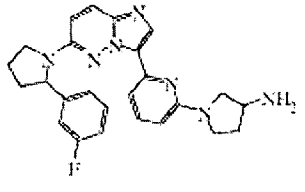
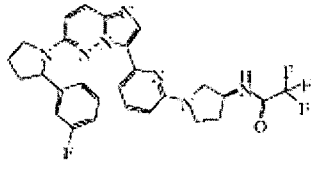
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
267		^{1}H RMN (400 MHz, DMSO-d6) 7.983 (s, 1H), 7.822 (d, J = 0.024, 1H), 7.459 – 7.281 (m, 3H), 7.101 – 7.081 (m, 2H), 6.966 (dt, J = 0.021, 0.005, 1H), 6.726 (br s, 1H), 6.272 (d, J = 0.021, 1H), 5.118 -5.098 (m, 2H), 3.976 – 3.901 (m, 2H), 3. 591 (q, J = 0.021, 1H), 3.522 (dd, J = 0.027, 0.009, 2H), 2.380 (m, 1H), 1.969 – 1.921 (m, 3H), 1.818 – 1.787 (m, 2H), 1.166 (m, 2H) MS (m/z): 461.5
268		^{1}H RMN (400 MHz, DMSO-d6) 7.981 (s, 1H), 7.823 (d, J = 0.025, 1H),

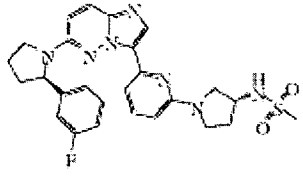
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		7.462 – 7.282 (m, 3H), 7.101 (m, 2H), 6.991 (dt, J = 0.022, 0.005, 1H), 6.725 (br s, 1H), 6.272 (d, J = 0.021, 1H), 5.119 (m, 2H), 3.977 – 3.901 (m, 2H), 3.614 (q, J = 0.021, 1H), 3.516 (dd, J = 0.028, 0.009, 2H), 2.380 (m, 1H), 2.001 – 1.921 (m, 3H), 1.831 – 1.792 (m, 2H), 1.167 (m, 2H) MS (m/z): 461.5
269		MS (m/z): 432.5
270		^{1}H RMN (400 MHz, DMSO-d6) 8.019 (s, 1H), 7.828 (d, J = 0.025, 1H), 7.507 – 7.282 (m, 3H),

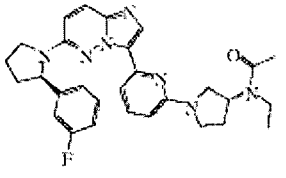
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		7.105 – 7.081 (m, 2H), 6.988 – 6.943 (m, 1H), 6.725 (br s, 1H), 6.356 (d, J = 0.021, 1H), 5.111 – 5.091 (m, 1H), 4.483 (p, J = 0.019, 1H), 3.952 – 3.900 (m, 1H), 3.649 – 3.572 (m, 1H), 3.441 – 3.400 (m, 1H), 3.359 – 3.305 (m, 2H), 2.921 (s, 3H), 2.714 (s, 3H), 2.170 – 2.041 (m, 2H), 2.002, 1.929 (m, 2H), 1.832 – 1.771 (m, 1H) MS (m/z): 536.6
271		MS (m/z): 461.5

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
272		MS (m/z): 500.6
273		MS (m/z): 516.6
274		MS (m/z): 479.5
275		MS (m/z): 514.6
276		MS (m/z): 530.6
277		MS (m/z): 522.6

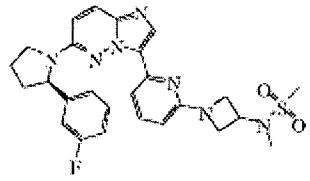
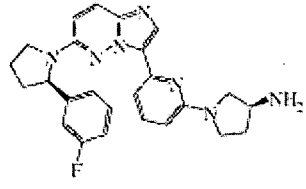
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
278		MS (m/z): 550.7
279		^{1}H RMN (400 MHz, DMSO-d6): 7.981 (s, 1H), 7.829 (d, J = 0.024, 1H), 7.741 (d, J = 0.02, 1H), 7.475 – 7.217 (m, 3H), 7.098 – 7.078 (m, 2H), 6.990 (dt, J = 0.022, 0.005, 1H), MS (m/z): 500.6
280		^{1}H RMN (400 MHz, DMSO-d6) 8.041 (s, 1H), 7.902 (d, J = 0.025, 1H), 7.476 – 7.265 (m, 3H), 7.169 (d, J = 0.02, 2H), 7.055 (t, J = 0.02, 1H), 6.824 (br s, 1H), 6.763 (d, J = 0.022, 1H), 5.177

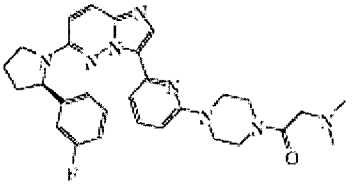
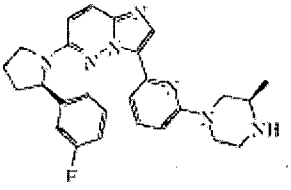
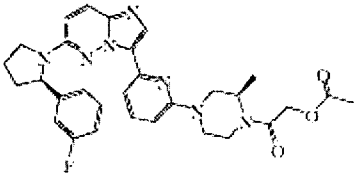
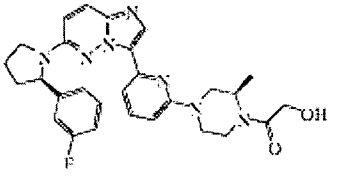
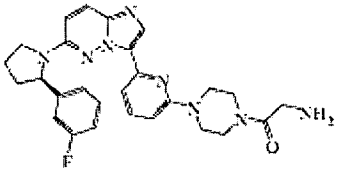
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(d, J = 0.20, 1H), 4.248 (d, J = 0.031, 1H), 4.018 – 3.967 (m, 1H), 3.701 (q, J = 0.021, 1H), 3.207 – 3.133 (m, 1H), 2.878 (t, J = 0.021, 1H), 2.070 – 1.998 (m, 3H), 1.888 – 1.830 (m, 2H), 1.477 – 1.292 (m, 3H), 0.988 (d, J = 0.016, 2H) MS (m/z): 473.6
281		MS (m/z): 444.5
282		MS (m/z): 540.5

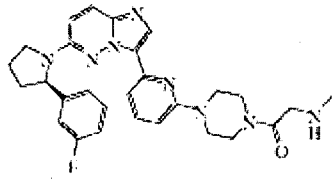
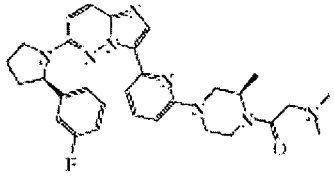
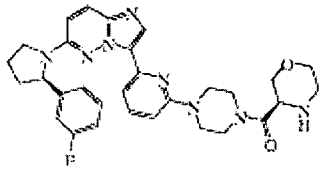
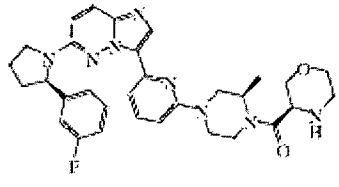
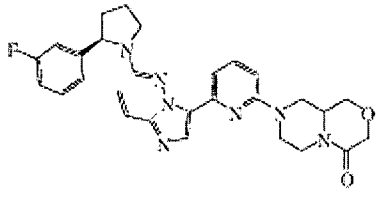
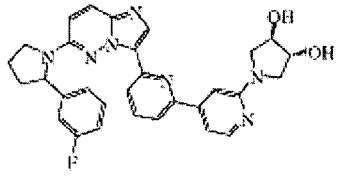
# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
283		^{1}H RMN (400 MHz, DMSO d6) 8.061 (s, 1H), 7.871 (d, J = 0.019, 1H), 7.386 – 7.287 (m, 3H), 7.102 – 7.081 (m, 2H), 6.992 (dt, J = 0.019, 0.004, 1H), 6.831 (br s, 1H), 6.343 (d, J = 0.023, 1H), 5.122 (dd, J = 0.02, 0.006, 1H), 4.108 – 3.908 (m, 2H), 3.713 (dd, J = 0.026, 0.010, 1H), 3.638 (q, J = 0.020, 1H), 3.536 – 3.478 (m, 1H), 3.375 (q, J = 0.018, 1H), 3.313 (dd, J = 0.027, 0.014, 1H), 2.409 – 2.359 (m, 1H), 2.223 (sexteto, J = 0.015, 1H), 2.009 – 1.776 (m, 4H) MS (m/z): 522.6

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
284		^{1}H RMN (400 MHz, DMSO-d6) 8.047 (d, J = 0.038, 1H), 7.893 (d, J = 0.025, 1H), 7.571 – 7.355 (m, 3H), 7.170 – 7.149 (m, 2H), 7.059 (dt, J = 0.019, 0.004, 1H), 6.802 (br s, 1H), 6.413 (t, J = 0.02, 0.006, 1H), 4.879 (p, J = 0.020, 1H), 4.622 (p, J = 0.020, 1H), 4.059 – 3.967 (m, 1H), 3.669 – 3.636 (m, 3H), 3.392 – 3.23 (m, 2H), 2.209 – 1.994 (m, 7H), 1.90 – 1.818 (m, 1H), 1.196 – 1.135 (m, 2H), 1.079 (t, J = 0.017, 2H) MS (m/z): 514.6

391

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
285		MS (m/z): 522.6
286		^{1}H RMN (400 MHz, DMSO-d6) 7.969 (s, 1H), 7.815 (d, J = 0.024, 1H), 7.397 – 7.279 (m, 3H), 7.096 – 7.069 (m, 2H), 6.984 (dt, J = 0.022, 0.006, 1H), 6.738 (br s, 1H), 6.256 (d, J = 0.020, 0.006, 1H=. 3.946 – 3.895 (m, 1H), 3.628 (q, J = 0.021, 1H), 3.515 – 3.439 (m, 3H), 3.374 – 3.314 (m, 1H), 2.405 – 2.355 (m, 1H), 2.018 – 1.922 (m, 3H), 1.827 – 1.766 (m, 3H), 1.666 (sexteto, J = 0.016, 1H)

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		MS (m/z): 444.5
287		MS (m/z): 529.6
288		MS (m/z): 458.5
289		MS (m/z): 558.6
290		MS (m/z): 516.6
291		MS (m/z): 501.6

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
292		MS (m/z): 515.6
293		MS (m/z): 543.7
294		MS (m/z): 557.6
295		MS (m/z): 571.7
296		MS (m/z): 514.6
297		^{1}H RMN (400 MHz, DMSO-d6) 8.472 (s, 1H), 8.165 (d, J = 0.019, 1H),

# Comp.	Estructura	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		8.003 – 7.976 (m, 2H), 7.888 (br s, 1H), 7.630 . 7.600 (m, 2H), 7.376 (q, J = 0.019, 1H), 7.148 (d, J = 0.019, 2H),7.010 (t, J = 0.019, 2H), 5.496 (br s, 2H), 5.160 (d, J = 0.017, 1H), 4.148 (d, J = 0.007, 2H), 7.007 – 3.953 (m, 1H), 3.806 (d, J = 0.022, 3H), 3.674 – 3.582 (m, 4H), 2.031 – 1.958 (m, 2H), 1.854 – 1.819 (m, 1H) MS (m/z): 538.6

ENSAYOS

Preparación de diluciones de compuestos

Los compuestos de prueba se disolvieron en sulfóxido de dimetilo (10 mM), y se transfirieron a tubos Matrix de fondo plano o en forma de V de 1.4 mililitros, portando un chip de matriz

bidimensional único mediante cubos de los compuestos individuales. Los números de estos chips se relacionaron distintivamente a los números de identificación de los compuestos individuales. Las soluciones de suministro se almacenaron a -20°C si no se utilizaron inmediatamente. Para el procedimiento de prueba, los frascos se descongelaron y se identificaron mediante un escáner, en donde se generó una hoja de cálculo que guió los siguientes pasos de procesamiento.

Las diluciones de compuestos se hicieron en placas de 96 pozos. Este formato hizo posible el ensayo de máximo 40 compuestos de prueba individuales en 8 concentraciones (puntos individuales), incluyendo 4 compuestos de referencia. El protocolo de dilución incluyó la producción de placas de pre-dilución, placas maestras, y placas de ensayo:

Placas de compuestos: Se transfirieron 30 microlitros de la solución del compuesto individual (10 mM) en sulfóxido de dimetilo (DMSO), incluyendo el compuesto estándar, a las columnas 1 y 13 de una placa de 384 pozos. Se agregaron 20 microlitros de sulfóxido de dimetilo (DMSO) al resto de los pozos, y los compuestos se diluyeron en serie (1:3) mediante la transferencia de 10 microlitros desde un pozo de la columna 1 ó 13 hasta el siguiente pozo de la columna 2 ó 13, respectivamente y sucesivamente con la ayuda de un robot Minitrack.

Placas de ensayo: Entonces se prepararon placas de ensayo idénticas mediante la adición de 50 nanolitros de cada una de las

diluciones de compuestos de las placas de compuestos a las "placas de ensayo" de 384 pozos. En lo siguiente, los compuestos se mezclaron con 50 microlitros de los componentes de ensayo (células o enzimas), y se probaron para determinar su actividad inhibidora.

Los compuestos de la fórmula (I) se ensayaron para medir su capacidad para inhibir las cinasas de proteína TrkA, TrkB, y/o TrkC. Se ensayaron otros compuestos de la fórmula (I) para medir su capacidad para inhibir un panel de cinasas, incluyendo, pero no limitándose a, las cinasas de proteína Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y/o ALK.

Efecto sobre la proliferación de diferentes células dependientes de cinasa

Los compuestos de la fórmula (I) se probaron para determinar su efecto anti-proliferativo sobre las células Ba/F3 que expresaban cualquiera de Tel-TrkA, Tel-TrkB, o Tel-TrkC, y un panel adicional de 34 cinasas diversas seleccionadas activadas mediante la fusión con los componentes de dimerización Bcr o Tel (Abl, AIK, BMX, EphA3, EphB2, FGFR2, FGFR3, FGFR4, FGR, FLT1, FLT3, FLT4, FMS, IGF1R, InsR, JAK1, JAK2, JAK3, KDR, Kit, Lck, Lyn, MER, MET, PDGFRb, RET, RON, Ros-1, Src, Aurora, TIE2, TYK2, Tie1, ZAP70). Se probó el efecto anti-proliferativo de estos compuestos sobre las diferentes líneas celulares y sobre las células no transformadas, en 12 concentraciones diferentes de los compuestos diluidos en serie 3 veces, en placas de 384 pozos, como se describe anteriormente (en

un medio que carecía de IL3). Los valores IC_{50} de los compuestos sobre las diferentes líneas celulares se determinaron a partir de las curvas de respuesta a la dosis.

Upstate KinaseProfiler^{MR} – Ensayo de enlace de filtro radioenzimático

Los compuestos de la fórmula (I) se evaluaron para determinar su capacidad para inhibir a los miembros individuales de un panel de cinasas (una lista parcial no limitante de cinasas incluye: las cinasas Abl, Aurora, cSrc, TPR-Met, Tie2, MET, FGFR3, Axl, Bmx, BTK, c-kit, CHK2, FLT3, MST2, p70S6K, PDGFR, PKB, PKCα, Raf, ROCK-II, Rsk1, SGK, TrkA, TrkB y TrkC, Ros, KDR, FMS, c-FMS, JAK2, JAK3, Lck, IGF-1R, ALK4, ALK5 y ALK). Los compuestos se probaron por duplicado en una concentración final de 10 µM siguiendo este protocolo genérico. Observe que la composición reguladora de cinasa y los sustratos varían para las diferentes cinasas incluidas en el panel "Upstate KinaseProfiler^{MR}". El regulador de cinasa (2.5 microlitros, 10x - que contenía $MnCl_2$ cuando se requirió), la cinasa activa (0.001-0.01 Unidades; 2.5 microlitros), el péptido específico o Poli(Glu4-Tyr) (de 5 a 500 µM o 0.01 miligramos/mililitro) en regulador de cinasa, y el regulador de cinasa (50 µM; 5 microlitros), se mezclaron en un Eppendorf sobre hielo. Se agregó una mezcla de Mg/ATP (10 microlitros; $MgCl_2$ 67.5 (ó 33.75) mM, ATP 450 (ó 225) µM, y 1 µCi/microlitro de [γ-^{32}P]-ATP (3,000 Ci/milimol)), y la reacción se incubó a aproximadamente 30°C durante aproximadamente 10 minutos. La mezcla de reacción se manchó (20

microlitros) sobre un cuadrado de papel P81 de 2 centímetros x 2 centímetros (fosfocelulosa, para los sustratos peptídicos positivamente cargados) o Whatman No. 1 (para el sustrato peptídico Poli (Glu4-Tyr)). Los cuadrados del ensayo se lavaron 4 veces, durante 5 minutos cada una, con ácido fosfórico al 0.75 por ciento, y se lavaron una vez con acetona durante 5 minutos. Los cuadrados del ensayo se transfirieron a un frasco de centelleo, se agregaron 5 mililitros de cóctel de centelleo, y se cuantificó la incorporación de ^{32}P (cpm) al sustrato peptídico con un contador de centelleo Beckman. Se calculó el porcentaje de inhibición para cada reacción.

Inhibición de la proliferación celular dependiente de TrkA, TrkB y TrkC

Los compuestos de la fórmula (I) se ensayaron para medir su capacidad para inhibir selectivamente la proliferación celular de las células Ba/F3 que expresaban TrkA, TrkB o TrkC activadas, a través de su fusión con el dominio de dimerización del factor de transcripción Tel (ETV6), así como de las células Ba/F3 que co-expresaban rTrkA y mNGF de longitud completa, comparándose con las células BaF3 progenitoras.

La línea celular utilizada fue la línea de células progenitoras hematopoiéticas de murino Ba/F3 que expresa luciferasa, transformada con los ADNcs humanos de Tel-TrkA, Tel-TrkB, o Tel-TrkC (Ba/F3 EN A/B/C). Estas células se mantuvieron en RPMI/suero fetal de becerro al 10 por ciento (RPMI/FCS) complementado con 50 miligramos/mililitro de penicilina, 50 miligramos/mililitro de

estreptomicina, y L-glutamina 200 mM. Las células Ba/F3 no transformadas se mantuvieron de una manera similar con la adición de 5 nanogramos/mililitro de IL3 recombinante de murino.

50 microlitros de una suspensión celular de Ba/F3 o Ba/F3 EN A/B/C se aplicaron a microplacas Greiner de 384 pozos (blancas), a una densidad de 2,000 células por pozo. A cada pozo se le agregaron 50 nanolitros del compuesto de prueba diluido en serie (solución 10-0.0001 mM en sulfóxido de dimetilo). Las células se incubaron durante 48 horas a 37°C, con CO_2 al 5 por ciento. A cada pozo se le agregaron 25 microlitros de sustrato de luciferasa Bright glo® (Promega). La luminiscencia emitida se cuantificó utilizando el sistema de luminiscencia ACQUEST^{MR} (Molecular Devices). Los valores IC_{50} se calcularon mediante análisis de regresión lineal del porcentaje de inhibición de cada compuesto en 12 concentraciones.

Inhibición de la actividad de cinasa celular de la Cinasa de Linfoma Anaplásico (ALK)

La inhibición de la actividad de cinasa de tirosina de ALK se demuestra empleando los métodos conocidos, por ejemplo utilizando el dominio de cinasa recombinante de la ALK en analogía al ensayo de cinasa VEGF-R descrito en J. Wood y colaboradores, Cancer Res. 60, 2178-2189 (2000). En general, se llevaron a cabo ensayos enzimáticos *in vitro* utilizando la cinasa de proteína tirosina de GST-ALK en placas de 96 pozos, como un ensayo de enlace de filtro en Tris-HCl 20 mM, pH = 7.5, $MgCl_2$ 3 mM, $MnCl_2$ 10 mM, DTT 1 mM, 0.1 µCi / ensayo (= 30 microlitros) de [γ-^{33}P]-ATP, ATP 2 µM, 3

microgramos/mililitro de poli-(Glu, Tyr, 4:1) Poli-EY (Sigma P-0275), sulfóxido de dimetilo al 1 por ciento, 25 nanogramos de enzima de ALK. Los ensayos se incubaron durante 10 minutos a temperatura ambiente. Las reacciones se terminaron mediante la adición de 50 microlitros de EDTA 125 mM, y la mezcla de reacción se transfirió a una placa MAIP Multiscreen (Millipore, Bedford, MA, EUA) previamente humedecida con metanol, y se rehidrató durante 5 minutos con H_2O. En seguida del lavado (H_3PO_4 al 0.5 por ciento), las placas se contaron en un contador de centelleo de líquidos. Los valores IC_{50} se calcularon mediante análisis de regresión lineal del porcentaje de inhibición.

Los compuestos de la fórmula (I) inhiben potentemente el crecimiento de las células de murino BaF3 que sobre-expresan NPM-ALK humana. La expresión de NPM-ALK se logra mediante la transfección de la línea celular BaF3 con un vector de expresión pCIneo^{MR} (Promega Corp., Madison WI, EUA) que codifica para NPM-ALK, y la subsiguiente selección de células resistentes a G418. Las células BaF3 no transfectadas dependen de IL-3 para la sobrevivencia celular. En contraste, las células BaF3 que expresan NPM-ALK (denominadas como BaF3-NPM-ALK posteriormente en la presente) pueden proliferar en ausencia de IL-3, debido a que obtienen la señal proliferativa a través de la cinasa NPM-ALK. Por consiguiente, los inhibidores supuestos de la cinasa NPM-ALK suprimen la señal de crecimiento, y dan como resultado la actividad anti-proliferativa. La actividad anti-proliferativa de los inhibidores

supuestos de la cinasa NPM-ALK, sin embargo, se puede superar mediante la adición de IL-3, la cual proporciona las señales de crecimiento a través de un mecanismo independiente de NPM-ALK. También se ha descrito un sistema celular análogo que utiliza la cinasa FLT3 (véase, E Weisberg y colaboradores, Cancer Cell; 1, 433-443 (2002)).

La actividad inhibidora de los compuestos de la fórmula (I) se determina como sigue. En general, las células BaF3-NPM-ALK (15,000/microlitro por pozo de la placa) se transfirieron a las placas de microtitulación de 96 pozos. Los compuestos de prueba disueltos en sulfóxido de dimetilo (DMSO) se agregaron en una serie de concentraciones (serie de dilución), de tal manera que la concentración final de sulfóxido de dimetilo no fuera mayor del 1 por ciento (volumen/volumen). Después de la adición, las placas se incubaron durante dos días, durante los cuales, los cultivos de control sin compuesto de prueba fueron capaces de experimentar dos ciclos de división celular. El crecimiento de las células BaF3-NPM-ALK se midió por medio de teñido YOPRO^{MR} [T. Idziorek y colaboradores, J. Immunol. Methods; 185: 249-258 (1995)]: 25 microlitros de regulador de lisis, el cual comprende citrato de sodio 20 mM, pH de 4.0, cloruro de sodio 26.8 mM, NP40 al 0.4 por ciento, EDTA 20 mM, y se agregaron 20 mM a cada pozo. La lisis celular se completó dentro de 60 minutos a temperatura ambiente, y se determinó la cantidad total de YOPRO^{MR} enlazado al ADN, mediante una medición utilizando el lector de 96 pozos Cytofluor II (PerSeptive

Biosystems) con las siguientes posiciones: Excitación (nanómetros) 485/20 y Emisión (nanómetros) 530/25.

Los valores IC_{50} se determinaron mediante un sistema auxiliado por computadora utilizando la fórmula: $IC_{50} = [(ABS_{prueba} - ABS_{inicial}) / (ABS_{control} - ABS_{inicial})] \times 100$. (ABS = absorción). El valor IC_{50} se dio como la concentración del compuesto de prueba en cuestión que dio como resultado un conteo celular que es el 50 por ciento más bajo que el obtenido utilizando el control sin inhibidor.

La acción antiproliferativa de los compuestos de la fórmula (I) también se determinó en la línea celular de linfoma humano KARPAS-299 (DSMZ Deutsche Sammiung von Mikroorganismen und Zelikulturen GmbH, Braunschweig, Alemania, descrita en WG Dirks y colaboradores, Int. J. Cancer 100, 49-56 (2002)) utilizando la misma metodología descrita anteriormente para la línea celular BaF3-NPM-ALK. En algunas modalidades, los compuestos de la fórmula (I) exhiben una actividad inhibidora con una IC_{50} en el intervalo de aproximadamente 0.01 a 1 µM. La acción de los compuestos de la fórmula (I) sobre autofosforilación de la ALK se determinó en la línea celular de linfoma humano KARPAS-299 por medio de un inmunomanchado, como se describe en WG Dirks y colaboradores, Int. J. Cancer 100, 49-56 (2002).

Inhibición de la proliferación celular dependiente de KDR

Los compuestos de la fórmula (I) se ensayaron para medir su capacidad para inhibir selectivamente la proliferación celular de las células Ba/F3 que expresaban la KDR activada a través de su fusión

con el dominio de dimerización del factor de transcripción Tel (ETV6), comparándose con las células BaF3 progenitoras.

Las células pro-B de murino Ba/F3 que expresaban luciferasa se transformaron con Tel-KDR. Las células se mantuvieron en RPMI/suero fetal de becerro al 10 por ciento (RPMI/FCS) complementado con 50 microgramos/mililitro de penicilina, 50 microgramos/mililitro de estreptomicina, y L-glutamina 200 mM. Las células Ba/F3 no transformadas se mantuvieron de una manera similar con la adición de IL3 recombinante de murino. Las células se dosificaron en una placa en formato de 384 pozos a 5,000 células / pozo en 50 microlitros del medio de cultivo. Los compuestos de la fórmula (I) se disolvieron y se diluyeron en sulfóxido de dimetilo (DMSO). Se hicieron diluciones en serie a 1:3 de doce puntos en sulfóxido de dimetilo (DMSO) para crear un gradiente de concentraciones en el intervalo desde 10 mM hasta 0.05 µM. Las células se agregaron con 50 nanolitros de los compuestos diluidos, y se incubaron durante 48 horas en una incubadora de cultivo celular. La señal luminiscente se midió en seguida de la adición del sustrato de luciferasa Bright glo® (Promega). Los valores IC_{50} se calcularon mediante análisis de regresión lineal del porcentaje de inhibición de cada compuesto en 12 concentraciones.

FLT-3 (Ensayo Enzimático)

El ensayo de la actividad de cinasa con la FLT-3 purificada (Upstate) se llevó a cabo en un volumen final de 10 microlitros conteniendo 0.25 microgramos/mililitro de enzima en regulador de

cinasa (Tris-HCl 30 mM, pH de 7.5, $MgCl_2$ 15 mM, $MnCl_2$ 4.5 mM, Na_3VO_4 15 µM, y 50 microgramos/mililitro de albúmina de suero bovino), y los sustratos (5 microgramos/mililitro de biotina-poli-EY(Glu, Tyr) (CIS-US, Inc.) y ATP 3 µM). Se hicieron dos soluciones: la primera solución de 5 microlitros que contenía la enzima FLT-3 en regulador de cinasa, se dosificó primeramente en una ProxiPlate® en formato de 384 pozos (Perkin-Elmer), seguido por la adición de 50 nanolitros de los compuestos disueltos en sulfóxido de dimetilo; luego se agregaron a cada pozo 5 microlitros de la segunda solución que contenía el sustrato (poli-EY) y ATP en regulador de cinasa. Las reacciones se incubaron a temperatura ambiente durante una hora, se interrumpieron mediante la adición de 10 microlitros de la mezcla de detección HTRF, la cual contenía Tris-HCl 30 mM, pH de 7.5, KF 0.5 M, ETDA 50 mM, 0.2 miligramos/mililitro de albúmina de suero bovino, 15 microgramos/mililitro de estreptavidina-XL665 (CIS-US, Inc.), y 150 nanogramos/mililitro de anticuerpo anti-fosfotirosina conjugado con criptato (CIS-US, Inc.). Después de una hora de incubación a temperatura ambiente para permitir la interacción de estreptavidina-biotina, se leyeron las señales fluorescentes resueltas en el tiempo en el Analyst GT (Molecular Devices Corp.). Los valores IC_{50} se calcularon mediante análisis de regresión lineal del porcentaje de inhibición de cada compuesto en 12 concentraciones (dilución de 1:3, desde 50 µM hasta 0.28 nM). En este ensayo, los compuestos de la fórmula (I) tienen una IC_{50} en el intervalo de 10 nM a 2 µM.

FLT-3 (Ensayo Celular)

Los compuestos de la fórmula (I) se probaron con el fin de determinar su capacidad para inhibir la proliferación celular de la Ba/F3-FLT3-ITD transformada, la cual depende de la actividad de cinasa celular de FLT-3. Las Ba/F3-FLT3-ITD se cultivaron hasta 800,000 células/mililitro en suspensión, con RPMI 1640 complementado con suero bovino fetal al 10 por ciento como el medio de cultivo. Las células se dosificaron en una placa de formato de 384 pozos a 5,000 células/pozo en 50 microlitros del medio de cultivo. Los compuestos de la fórmula (I) se disolvieron y se diluyeron en sulfóxido de dimetilo (DMSO). Se hicieron diluciones en serie de doce puntos a 1:3 en sulfóxido de dimetilo (DMSO), para crear un gradiente de concentraciones en el intervalo típicamente de 10 mM a 0.05 µM. Las células se agregaron a 50 nanolitros de los compuestos diluidos, y se incubaron durante 48 horas en una incubadora de cultivo celular. Se agregó AlamarBlue® (TREK Diagnostic Systems), el cual se puede utilizar para monitorear el medio ambiente reductor creado por las células en proliferación, y se agregaron las células en una concentración final del 10 por ciento. Después de cuatro horas adicionales de incubación en una incubadora de cultivo celular a 37°C, se cuantificaron las señales de fluorescencia a partir del AlamarBlue® reducido (Excitación a 530 nanómetros, Emisión a 580 nanómetros) en el Analyst GT (Molecular Devices Corp.). Los valores IC_{50} se calcularon mediante análisis de regresión lineal del porcentaje de inhibición de cada compuesto en

12 concentraciones.

c-Kit – Ensayo de proliferación

Los compuestos se probaron con el fin de determinar su capacidad para inhibir la proliferación de las células Ba/F3 de tipo silvestre, y de las células Ba/F3 transformadas con las cinasas de tirosina fusionadas con Tel c-Kit. Las células Ba/F3 no transformadas se mantuvieron en un medio que contenía IL3 recombinante. Las células se aplicaron en placas TC de 384 pozos a 5,000 células en 50 microlitros del medio por pozo, y se agregó el compuesto de prueba de 0.06 nM a 10 µM. Las células se incubaron entonces durante 48 horas a 37°C, con CO_2 al 5 por ciento. Después de incubar las células, se agregaron 25 microlitros de BRIGHT GLO® (Promega) a cada pozo, siguiendo las instrucciones del fabricante, y las placas se leyeron utilizando el Analyst GT – Modo de Luminiscencia – 50,000, tiempo de integración en RLU. Los valores IC_{50}, la concentración del compuesto requerida para la inhibición del 50 por ciento, se determinaron a partir de una curva de respuesta a la dosis.

Ensayo de cKit – Mo7e

Los compuestos descritos en la presente se probaron para determinar la inhibición de la proliferación dependiente de SCF, utilizando células Mo7e, las cuales expresaban endógenamente c-kit, en un formato de 96 pozos. Dicho de una manera breve, se evaluaron los compuestos de prueba diluidos en serie dos veces (Cmax = 10µM), para determinar la actividad anti-proliferativa de las

células Mo7e estimuladas con SCF humano recombinante. Después de 48 horas de incubación a 37°C, se midió la viabilidad celular utilizando un ensayo colorimétrico MTT de Promega.

Descripción del ensayo bioquímico para DNA-PK:

El ensayo se conduce utilizando el kit V7870 de Promega (SignaTECT® Sistema de Cinasa de Proteína Dependiente del ADN, que comprende DNA-PK, ingredientes adicionales de extremo de sustrato peptídico biotinilado, Promega, Madison, Wisconsin, EUA), que cuantifica la actividad de cinasa de proteína dependiente del ADN, tanto en preparaciones enzimáticas purificadas como en extractos nucleares celulares. DNA-PK es una cinasa de proteína serina/treonina que requiere del ADN de doble cadena (ADNds) para su actividad. El enlace del ADNds con la enzima da como resultado la formación de la enzima activa, y también lleva al sustrato más cerca de la enzima, permitiendo que proceda la reacción de fosforilación.

El regulador de reacción X5 de DNA-PK (HEPES 250 mM, KCl 500 mM, $MgCl_2$ 50 mM, EGTA 1 mM, EDTA 0.5 mM, DTT 5 mM, pH hasta 7.5 con KOH) se diluye a 1/5 en agua desionizada, y se agrega albúmina de suero bovino (suministro = 10 miligramos/mililitro) hasta una concentración final de 0.1 miligramos/mililitro.

El regulador de activación se hace a partir de 100 microgramos/mililitro de ADN de timo de becerro en regulador de control (Tris-HCl 10 mM (pH de 7.4), EDTA 1 mM (pH de 8.0)). Por cada tubo, la mezcla de reacción se compone de: 2.5 microlitros de

reguladores de activación o de control, 5 microlitros de regulador de reacción X5, 2.5 microlitros de sustrato peptídico biotinilado derivado de p53 (suministro = 4mM), 0.2 microlitros de albúmina de suero bovino (suministro a 10 miligramos/mililitro), y 5 microlitros de [γ-^{32}P] ATP (5 microlitros de ATP frío 0.5 mM + 0.05 microlitros de Redivue [γ-^{32}P] ATP = Amersham AA0068-250 µCi, 3000Ci/milimol, 10 µCi/microlitro (ahora GE Healthcare Biosciences AB, Uppsala, Suecia).

La enzima DNA-PK (Promega V5811, concentración = 100 Unidades/microlitro) se diluye a 1/10 en regulador de reacción X1, y se mantiene sobre hielo hasta su uso inminente. 10.8 microlitros de la enzima diluida se incuban con 1.2 microlitros de los compuestos 100 µM (diluidos a 1/100 en agua a partir del suministro 10 mM en sulfóxido de dimetilo puro) durante 10 minutos, a temperatura ambiente. Durante ese tiempo, se agregan 15.2 microlitros de la mezcla de reacción a tubos con tapa de rosca detrás de un vidrio Perspex. Entonces se transfieren 9.8 microlitros de la enzima a los tubos que contienen la mezcla de reacción, y después de 5 minutos de incubación a 30°C, la reacción se detiene mediante la adición de 12.5 microlitros de regulador de terminación (clorhidrato de guanidina 7.5 M).

Después de mezclar bien, se aplica una alícuota de 10 microlitros de cada tubo a una membrana de captura de biotina SAM2® (Promega, Madison, Wisconsin, EUA), la cual se deja secar durante unos cuantos minutos. Entonces la membrana se lava extensamente para remover el exceso de [γ-^{32}P] ATP libre y

proteínas no biotiniladas: una vez durante 30 segundos en 200 mililitros de NaCl 2M, 3 veces durante 2 minutos cada una, en 200 mililitros de NaCl 2M, 4 veces durante 2 minutos cada una, en NaCl 2M en H_3PO_4 al 1 por ciento, y dos veces durante 30 segundos cada una, en 100 mililitros de agua desionizada. La membrana subsiguientemente se deja secar al aire a temperatura ambiente durante 30 a 60 minutos.

Cada cuadrado de membrana se separa utilizando fórceps y tijeras, y se coloca en un frasco de centelleo, después de lo cual, se agregan 8 mililitros de líquido de centelleo (Flo-Scint 6013547 de Perkin-Elmer). Entonces se determina la cantidad de ^{32}P incorporado en el sustrato peptídico biotinilado de DNA-PK mediante conteo de centelleo de líquidos.

Protocolo para la detección de fosfo-PKB en células U87MG mediante ELISA:

La eficacia de los compuestos de la fórmula (I) para bloquear la activación de la senda de PI3K/PKB se puede demostrar en establecimientos celulares como sigue: Las células U87MG (glioblastoma humano, ATCC No. HTB-14) se tripsinizaron, se contaron en un contador de células CASY (Sistemas Schärffe, Göttingen, Alemania), se diluyeron en un medio alto en glucosa de DMEM completo fresco, para cargar, por pozo, 150 microlitros de suspensión celular que contenía 4 x 10^4 células, y las placas de prueba se incubaron durante 18 horas. En paralelo, se cargaron 50 microlitros de anticuerpo de recubrimiento, a la concentración

deseada en PBS/O en cada pozo de las placas ELISA, y las placas se mantuvieron durante 2 horas a temperatura ambiente. Estos ensayos ELISA se llevaron a cabo en placas negras de 96 pozos de fondo plano (Microtest™, Falcon Becton-Dickinson, Ref: 353941) selladas con Selladores de Placas (Costar-Corning, Ref: 3095). El medio de las placas se desechó y fue reemplazado por medio alto en glucosa de DMEM completo que contenía ya sea sulfóxido de dimetilo al 0.1 por ciento, o bien el inhibidor al 0.1 por ciento, en titulaciones (7) de entre 10 mM y 0.156 mM en sulfóxido de dimetilo. Después de 30 minutos de contacto, se removió rápidamente el medio mediante aspiración, y entonces las placas se colocaron sobre hielo, e inmediatamente se lisaron las células con 70 microlitros de regulador de lisis. En paralelo, las placas de 96 pozos preparadas con el anticuerpo de recubrimiento (diluido a 1/250 (en PBS/O) Anti-Akt1 C-20, cabra, Santa-Cruz-1618, Santa Cruz Biotechnology, Inc., Santa Cruz, California, EUA) se lavaron 3 veces durante 1 minuto con PBS/O que contenía Tween 20 al 0.05 por ciento y Top-Block® al 0.1 por ciento (derivado de gelatina que bloquea los sitios de enlace no específicos sobre las superficies; Sigma-Aldrich, Fluka, Buchs, Suiza, Ref.: 37766), y los sitios de enlace de proteína restantes se bloquearon para impedir las interacciones no específicas, con 200 microlitros de suero regulado con fosfato que contenía Top Block® al 3 por ciento, durante 2 horas a temperatura ambiente. El contenido del pozo fue reemplazado con 50 microlitros de muestras a partir de las células tratadas, y las placas se incubaron durante 3 horas a 4°C.

Los ensayos ELISA se hicieron siempre en paralelo con los siguientes controles, en 6 réplicas: U87MG (control no tratado) o regulador de lisis solo (LB). Después de 3 lavados de 15 minutos, todos los pozos recibieron 50 microlitros del anticuerpo secundario (diluido a 1/250 (en Top Block al 3 por ciento) Anti-S473P-PKB, conejo, Cell Signaling-9271, Cell Signaling Technologies, Inc., Danvers, Massachusetts, EUA)), y se incubaron durante 16 horas a 4°C. Después de tres lavados, las placas se incubaron con el tercer anticuerpo conjugado (diluido a 1/1000 (en Top Block al 3 por ciento) anti-conejo (HRP) Jackson Immuno Research 111-035-144) durante 2 horas a temperatura ambiente. Finalmente, los inmuno-complejos se lavaron 2 veces durante 15 segundos con PBS/O/ Tween20 /Top Block, 1 vez con 200 microlitros de agua, y finalmente se dejaron 200 microlitros de agua en cada pozo de prueba antes de una incubación durante 45 minutos en la oscuridad. Las placas entonces se ensayaron con (sustrato quimiluminiscente ELISA pico SuperSignal®, Pierce, Ref: 27070, Pierce Biotechnology, Inc., Rockford, Illinois, EUA). Se agregaron 100 microlitros de sustrato, y las placas se agitaron durante 1 minuto. La luminiscencia se leyó inmediatamente en un luminómetro Top-Count NXT (Packard Bioscience).

También hubo experimentos que demostraron la actividad anti-tumoral de los compuestos de la fórmula (I) *in vivo*.

Por ejemplo, los ratones nu/nu atímicos Harlan hembras (Indianápolis, Indiana, EUA) con tumores U87MG de glioblastomas

humanos trasplantados subcutáneamente, se pueden utilizar para determinar la actividad anti-tumoral de los inhibidores de cinasa PI3. En el día 0, con los animales bajo narcosis con peroral Forene® (1-cloro-2,2,2-trifluoro-etil-difluoro-metil-éter, Abbot, Wiesbaden, Alemania), se coloca un fragmento de tumor de aproximadamente 25 miligramos bajo la piel del flanco izquierdo de los animales, y la pequeña herida cortada se cierra por medio de clips de sutura. Cuando los tumores alcanzan un volumen de 100 milímetros cúbicos, los ratones se dividen en grupos aleatorios de 6 a 8 animales, y comienza el tratamiento. El tratamiento se lleva a cabo durante un período de 2 a 3 semanas con la administración intravenosa o intraperitoneal de peroral una vez al día (o con menos frecuencia) de un compuesto de la fórmula (I) en un vehículo adecuado, en dosis definidas. Los tumores se midieron dos veces a la semana con un calibre de hoja, y se calculó el volumen de los tumores.

Como una alternativa a la línea celular U87MG, también se pueden utilizar otras líneas celulares de la misma manera, por ejemplo, la línea celular de adenocarcinoma de mama MDA-MB 468 (ATCC No. HTB 132; véase también In vitro 14, 911-15 [1978]); la línea celular de carcinoma de mama MDA-MB 231 (ATCC No. HTB-26; véase también In vitro 12, 331 [1976]); la línea celular de carcinoma de mama MDA-MB 453 (ATCC No.HTB-131); la línea celular de carcinoma de colon Colo 205 (ATCC No. CCL 222; véase también Cancer Res. 38, 1345-55 [1978]); la línea celular de carcinoma de próstata DU145 (ATCC No. HTB 81; véase también

Cancer Res. 37, 4049-58 [1978]), la línea celular de carcinoma de próstata PC-3 (preferida especialmente; ATCC No. CRL 1435; véase también Cancer Res. 40, 524-34 [1980]), y la línea celular de carcinoma de próstata PC-3M; la línea celular de adenocarcinoma de pulmón humano A549 (ATCC No. CCL 185; véase también Int. J. Cancer 17, 62-70 [1976]), la línea celular NCI-H596 (ATCC No. HTB 178; véase también Science 246, 491-4 [1989]); la línea celular de cáncer pancreático SUIT-2 (véase Tomioka y colaboradores, Cancer Res. 61, 7518-24 [2001]).

Actividad de cinasa de ALK5

La actividad de cinasa de ALK5 se evalúa midiendo la incorporación de fosfato radiomarcado [^{33}P] en el sustrato genérico, caseína. El dominio de cinasa de la ALK5 humana (aminoácidos 200-503) se fusiona con una marca de histidina N-terminal. La actividad de cinasa de ALK5 se hace constitutiva por medio de una mutación puntual en el aminoácido 204 (modificación de treonina hasta aspartato, ALK5 T204D), y la construcción de cinasa se diseña para expresarse a partir de una construcción de expresión de baculovirus en células de insectos. La proteína ALK5 T204D marcada con histidina recombinantemente expresada, purificada, se disuelve a 5.4 miligramos/mililitro en Tris-HCl 50 mM, pH de 8.0, NaCl 150 mM, DTT 5 mM. La ALK5 T204D se disuelve hasta 2.5 microgramos/mililitro en regulador de ensayo (regulador de ensayo: Tris-HCl 20 mM, pH de 7.4, $MgCl_2$ 10 mM, $MnCl_2$ 2 mM), en el día del uso.

Los compuestos de prueba y los compuestos de referencia se

disolvieron en el regulador de ensayo sin DTT, conteniendo sulfóxido de dimetilo al 5 por ciento (volumen/volumen). Las soluciones de suministro de los compuestos de prueba y de referencia se diluyeron en regulador de ensayo con DTT (1.25 mM) conteniendo sulfóxido de dimetilo al 4.5 por ciento (volumen/volumen). Se agregaron 10 mililitros del compuesto de prueba o de referencia a los pozos apropiados de una placa de fondo en U de 96 pozos. La actividad enzimática total se determina midiendo la actividad de ALK5 T204D en ausencia de los compuestos inhibidores de cinasa ALK5 de referencia. El enlace no específico (NSB) se determina midiendo la actividad de ALK5 T204D en la presencia de los compuestos de referencia inhibidores de cinasa ALK5. Se agregan 10 microlitros de solución de suministro de caseína desfosforilada (la caseína desfosforilada se disuelve en ddH_2O a 20 miligramos/mililitro) por pozo (concentración de ensayo final de 200 microgramos/pozo). Se agregan 20 microlitros de ALK5 T204D (solución de 2.5 microgramos/mililitro) por pozo (concentración de ensayo final de 50 nanogramos/pozo). Las placas se dejaron incubándose a temperatura ambiente durante 10 minutos.

Se agregan 10 microlitros de mezcla de ATP al pozo para iniciar la reacción ([^{33}P]ATP 0.66 nM/ATP no marcado 1 µM/concentración de ensayo final del pozo). La mezcla de ATP se prepara como sigue: El ATP no marcado (3 mM) se disuelve en ddH_2O, y se ajusta el pH a 7.4. La concentración de suministro de [^{33}P]ATP es de 10 µCi/microlitro. Se agrega el volumen de [^{33}P]ATP

apropiado a la solución de ATP no marcado, de tal manera que la concentración del ensayo final por pozo es de 0.1 µCi. En seguida de la adición de la mezcla de ATP, las placas se incubaron a temperatura ambiente durante 50 minutos. La reacción de cinasa se termina mediante la adición de 50 microlitros de Regulador de Paro (Tris-HCl 20 mM, pH de 7.4, EDTA 10 mM).

Se transfirieron 75 microlitros/pozo de la placa de reacción a una placa Multiscreen-IP (las placas Multiscreen IP se prepararon agregando 50 microlitros de etanol al 70 por ciento (volumen/volumen) por pozo, y se incubaron durante 5 minutos a temperatura ambiente. El etanol se removió mediante aspiración mediante una unidad de múltiple de vacío Multiscreen HTS (Millipore, Cat. No. MSVMHT500). Las placas se lavaron dos veces agregando 200 microlitros/pozo de ddH_2O). Las placas Multiscreen IP se incubaron a temperatura ambiente durante 30 minutos para permitir el enlace de la caseína a la placa. Las placas Multiscreen IP se lavaron tres veces agregando 200 microlitros/pozo de solución de ácido fosfórico 100 mM, y se removió cuidadosamente el empaque de la parte posterior de las placas Multiscreen IP, y las placas se secaron en el horno durante 30 minutos. Las placas Multiscreen IP se volvieron a sellar, y se agregaron 50 microlitros de Microscint^{MR}20, y luego las placas se sellaron en la parte superior, y se detectó y se cuantificó la caseína radiomarcada en un lector de placas TopCount^{MR} utilizando el protocolo de centelleo de ^{33}P.

Ensayos de perfilación de la familia de cinasa JAK/TYK

La eficacia de los compuestos de la fórmula (I) como inhibidores de la actividad de cinasa JAK/TYK se puede demostrar como sigue:

Se utilizaron las cuatro cinasas de la familia de cinasa JAK/TYK como proteínas de fusión con GST recombinantes purificadas, que contenían los dominios activos de cinasa. Se expresaron GST-JAK1(866-1154), GST-JAK3(811-1124), y GST-TYK2(888-1187), y se purificaron mediante cromatografía por afinidad. GST-JAK2(808-1132) se adquirió en Invitrogen (Carlsbad, EUA, #4288).

Los ensayos de cinasa se basaron en el ensayo de cambio de movilidad de Caliper utilizando los sistemas LabChip 3000. Esta tecnología es similar a la electroforesis capilar y utiliza separación del sustrato y el producto impulsada por la carga en un chip microfluídico.

Todas las reacciones de cinasa se llevaron a cabo en placas de microtitulación de 384 pozos en un volumen de reacción total de 18 microlitros. Las placas de ensayo se prepararon con 0.1 microlitros por pozo del compuesto de prueba en la concentración de prueba apropiada, como se describe bajo la sección "Preparación de diluciones de compuestos". Las reacciones se iniciaron mediante la combinación de 9 microlitros de mezcla de sustrato (consistente en péptido y ATP) con 9 microlitros de dilución de cinasa. Las reacciones se incubaron durante 60 minutos a 30°C y se detuvieron

mediante la adición de 70 microlitros de regulador de paro (Hepes 100 mM, sulfóxido de dimetilo al 5 por ciento, reactivo de recubrimiento al 0.1 por ciento, EDTA 10 mM, Brij 35 al 0.015 por ciento).

Se utilizaron péptidos sintéticos fluorescentemente marcados como sustratos en todas las reacciones. Se utilizó un péptido derivado a partir de la secuencia de IRS-1 (péptido IRS-1, FITC-Ahx-KKSRGDYMTMQIG-NH_2 para JAK1 y TYK2, y un péptido denominado como JAK3tide (FITC-GGEEEEYFELVKKKK-NH_2 para JAK2 y JAK3. Las condiciones específicas del ensayo se describen en la Tabla A:

Tabla A

Condiciones de ensayo de los ensayos de las cinasas individuales

Cinasa	JAK1	JAK2	JAK3	TYK2
Regulador	Hepes 50 mM pH 7.5, Tween 20 al 0.02%, DTT 1 mM, BSA al 0.02%, $MgCl_2$ 12 mM	Hepes 50 mM pH 7.5, Tween 20 al 0.02%, DTT 1 mM, BSA al 0.02%, $MgCl_2$ 9 mM	Hepes 50 mM pH 7.5, Tween 20 al 0.02%, DTT 1 mM, BSA al 0.02%, $MgCl_2$ 1.5 mM	Hepes 50 mM pH 7.5, Tween 20 al 0.02%, DTT 1 mM, BSA al 0.02%, $MgCl_2$ 9 mM
DMSO	0.6 %	0.6 %	0.6 %	0.6 %
Cinasa	50 nM	1.8 nM	6 nM	40 nM

Cinasa	JAK1	JAK2	JAK3	TYK2
conc.				
Substrato de péptido conc.	5 µM	2 µM	2 µM	5 µM
ATP conc.	40 µM	20 µM	80 µM	30 µM

Las reacciones terminadas se transfirieron al lector Caliper LabChip 3000, y se midió el cambio de cada reacción mediante la determinación de la proporción de sustrato/producto.

Ensayos de perfilación de cinasa-PI3

La eficacia de los compuestos de la fórmula (I) como inhibidores de cinasa-PI3 se demuestra como sigue: La reacción de cinasa se llevó a cabo en un volumen final de 50 microlitros por pozo de una placa de 96 pozos COSTAR de media área. Las concentraciones finales de ATP y fosfatidil-inositol en el ensayo fueron de 5 µM y 6 microgramos/mililitro, respectivamente. La reacción se inició mediante la adición de cinasa-PI3 p110ß. Los componentes del ensayo se agregaron por pozo como sigue:

- 10 microlitros del compuesto de prueba en sulfóxido de dimetilo al 5 por ciento por pozo en las columnas 2-1.
- La actividad total se determinó mediante la adición de 10 microlitros del 5 por ciento por volumen/volumen de sulfóxido de

dimetilo a los primeros 4 pozos de la columna 1 y a los últimos 4 pozos de la columna 12.

- El fondo se determinó mediante la adición del compuesto de control 10 µM a los últimos 4 pozos de la columna 1 y a los primeros 4 pozos de la columna 12.
- Se prepararon 2 mililitros de 'Mezcla de Ensayo' por placa:
  - 1.912 mililitros de regulador de ensayo HEPES;
  - 8.33 microlitros de suministro 3 mM de ATP, dando una concentración final de 5 µM por pozo;
  - 1 microlitro de [^{33}P]ATP en la fecha de actividad, dando 0.05 µCi por pozo;
  - 30 microlitros de 1 miligramo/mililitro de suministro de PI, dando una concentración final de 6 microgramos/mililitro por pozo;
  - 5 microlitros de suministro 1 M de $MgCl_2$, dando una concentración final de 1 mM por pozo;
  - Se agregaron 20 microlitros de la mezcla de ensayo por pozo.
- Se prepararon 2 mililitros de la 'Mezcla Enzimática' por placa (x* microlitros de cinasa-PI3 p110ß en 2 mililitros de regulador de cinasa). La 'Mezcla Enzimática' se mantuvo sobre hielo durante la adición a las placas de ensayo.
- Se agregaron 20 microlitros de la 'Mezcla Enzimática' por pozo para iniciar la reacción.

- La placa entonces se incubó a temperatura ambiente durante 90 minutos.
- La reacción se terminó mediante la adición de 50 microlitros de una suspensión de perlas WGA-SPA (perlas de Ensayo de Proximidad de Centelleo recubiertas con aglutinina de germen de trigo) por pozo.
- La placa de ensayo se selló utilizando un sello térmico TopSeal-S para microplacas de poliestireno (PerkinElmer LAS (Deutschland) GmbH, Rodgau, Alemania), y se incubó a temperatura ambiente durante cuando menos 60 minutos.
- La placa de ensayo entonces se centrifugó a 1,500 revoluciones por minuto durante 2 minutos, utilizando el centrífugo de banco Jouan (Jouan Inc., Nantes, Francia).
- La placa de ensayo se contó utilizando un Packard TopCount, contándose cada pozo durante 20 segundos.
- El volumen de enzima depende de la actividad enzimática del lote en uso.

Algunos de los compuestos muestran cierto nivel de selectividad contra los diferentes parálogos de PI3K alfa, beta, gamma y delta.

Ciertos Resultados de Ensayo

Diferentes compuestos de la fórmula (I) en forma libre o en forma de sal farmacéuticamente aceptable, exhiben propiedades farmacológicas, por ejemplo, como se indica mediante las pruebas *in vitro* e *in vivo* descritas en esta solicitud. El valor IC_{50} en estos

experimentos se da como la concentración del compuesto de prueba en cuestión que da como resultado un conteo celular que es el 50 por ciento más bajo que el obtenido utilizando el control sin inhibidor. En ciertos ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 1 nM a 200 μM. En algunos ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 μM a 100 μM.

En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 μM a 50 μM. En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 μM a 25 μM. En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 μM a 20 μM. En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 μM a 15 μM. En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 μM a 10 μM. En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 μM a 5 μM. En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 μM a 2 μM. En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 μM a 1 μM. En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 μM a 0.8 μM. En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 μM a 0.6 μM. En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 μM a 0.4 μM. En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 μM a 0.2 μM. En otros ejemplos, los

compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 µM a 0.1 µM. En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 µM a 0.08 µM. En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 µM a 0.06 µM. En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 µM a 0.04 µM. En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 µM a 0.02 µM. En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.001 µM a 0.01 µM.

En algunos ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.01 µM a 5 µM. En otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de 0.01 µM a 1 µM. En todavía otros ejemplos, los compuestos de la fórmula (I) tienen valores IC_{50} de menos de 1 nM. En ciertas modalidades, los compuestos de la fórmula (I) exhiben un porcentaje de inhibición mayor del 50 por ciento, o en otras modalidades, los compuestos de la fórmula (I) exhiben un porcentaje de inhibición mayor de aproximadamente el 70 por ciento, contra una o más de las siguientes cinasas a 10 µM: las cinasas Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-IR, ALK4, ALK5 y/o ALK.

A manera de ejemplo solamente, el compuesto de (R)-l-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-l-il)-imidazo-[l,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-piperidin-4-ol (véase el Ejemplo 16-4) tiene una IC_{50} de 4.41 µM, 0.0052 µM, 0.012 µM, 0.013 µM, en los ensayos celulares de BaF_3, BaF_3/Tel-TrkA, BaF_3/Tel-TrkB y BaF_3/TrkA-NFG CTG,

respectivamente.

A manera de ejemplo solamente, el compuesto de (R)-1-(4-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-l-il)-imidazo-[l,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-pirrolidin-3-ol (véase el Ejemplo 14-4) tiene una IC_{50} de 4.07 μM, 0.0022 μM, 0.0033 μM, 0.0042 μM, en los ensayos celulares de BaF_3, BaF_3/Tel-TrkA, BaF_3/Tel-TrkB y BaF_3/TrkA-NFG CTG, respectivamente.

A manera de ejemplo solamente, la IC_{50} para la inhibición de TrkA, TrkB, TrkC mediante ciertos compuestos de la fórmula (I) se enlistan en la siguiente Tabla 8. La identificación de cada compuesto de la Tabla 8 corresponde al Número de Tabla en donde el se enlista anteriormente el compuesto, y el número de compuesto respectivo.

Tabla 8

No. Tabla/ No. Comp.	Ba/F3 IC50 (μM)	Ba/F3 Tel-TrkA IC50 (μM)	Ba/F3 Tel-TrkB IC50 (μM)	Ba/F3 Tel-TrkC IC50 (μM)	Ba/F3 TRKA-NGF CTG IC50 (μM)	KM12 luc IC50 (μM)
Tabla 1-Comp. 1	15.95	0.21	0.15	0.069	0.68	0.23
Tabla 1-Comp. 31	>10	0.028	0.022	0.018	0.45	0.037
Tabla 1-Comp. 4	- - -	1.60	0.79	- - -	- - -	- - -

No. Tabla/ No. Comp.	Ba/F3 IC50 (μM)	Ba/F3 Tel-TrkA IC50 (μM)	Ba/F3 Tel-TrkB IC50 (μM)	Ba/F3 Tel-TrkC IC50 (μM)	Ba/F3 TRKA-NGF CTG IC50 (μM)	KM12 luc IC50 (μM)
Tabla 1-Comp. 5	>10	5.67	4.17	2.61	3.58	2.29
Tabla 2-Comp. 1	>9.69	0.013	0.0055	- - -	0.029	0.0070
Tabla 2-Comp. 4	>10	0.0086	0.0058	- - -	0.029	0.0070
Tabla 2-Comp. 6	>10	0.058	0.044	- - -	0.017	0.0083
Tabla 2-Comp. 7	>10	0.083	0.23	- - -	0.55	0.14
Tabla 2-Comp. 8	>10	0.0016	0.0022	- - -	0.029	0.0052
Tabla 2-Comp. 10	>10	0.0069	0.0062	- - -	0.0088	- - -
Tabla 2-Comp. 16	>7.67	0.10	0.12	- - -	0.14	- - -

No. Tabla/ No. Comp.	Ba/F3 IC50 (μM)	Ba/F3 Tel-TrkA IC50 (μM)	Ba/F3 Tel-TrkB IC50 (μM)	Ba/F3 Tel-TrkC IC50 (μM)	Ba/F3 TRKA-NGF CTG IC50 (μM)	KM12 luc IC50 (μM)
Tabla 2-Comp. 18	>10	0.036	0.036	- - -	0.056	0.022
Tabla 2-Comp. 19	5.05	2.17	1.70	- - -	1.42	- - -
Tabla 2-Comp. 20	>10	0.39	0.39	- - -	0.28	- - -
Tabla 2-Comp. 23	>10	0.01	0.024	- - -	0.012	- - -
Tabla 3-Comp. 1	>10	2.31	0.47	0.24	1.73	0.19
Tabla 3-Comp.	>10	1.33	0.95	0.21	0.62	0.90
Tabla 3-Comp. 6	>10	0.36	0.76	0.18	0.54	0.38
Tabla 3-Comp. 7	5.03	0.035	0.052	0.020	0.027	0.023

No. Tabla/ No. Comp.	Ba/F3 IC50 (μM)	Ba/F3 Tel-TrkA IC50 (μM)	Ba/F3 Tel-TrkB IC50 (μM)	Ba/F3 Tel-TrkC IC50 (μM)	Ba/F3 TRKA-NGF CTG IC50 (μM)	KM12 luc IC50 (μM)
Tabla 3-Comp. 10	>10	0.20	0.10	0.040	0.18	0.094
Tabla 3-Comp. 11	>10	0.087	0.056	0.017	0.074	0.036
Tabla 3-Comp. 18	7.23	0.013	0.010	0.0014	0.020	0.024
Tabla 3-Comp. 19	>10	1.02	0.54	- - -	0.37	- - -
Tabla 3-Comp. 26	>10	1.02	0.54	- - -	0.37	- - -
Tabla 3-Comp. 27	>10	0.14	0.093	- - -	0.32	- - -
Tabla 3-Comp. 30	>10	1.10	1.06	- - -	1.34	- - -
Tabla 3-Comp. 34	>10	1.20	0.40	0.13	0.50	0.010

No. Tabla/ No. Comp.	Ba/F3 IC50 (μM)	Ba/F3 Tel-TrkA IC50 (μM)	Ba/F3 Tel-TrkB IC50 (μM)	Ba/F3 Tel-TrkC IC50 (μM)	Ba/F3 TRKA-NGF CTG IC50 (μM)	KM12 luc IC50 (μM)
Tabla 3-Comp. 41	0.2	0.20	0.21	- - -	0.11	- - -
Tabla 3-Comp. 44	>10	1.12	1.14	- - -	1.20	- - -
Tabla 3-Comp. 45	8.059	1.02	0.79	- - -	1.02	- - -
Tabla 3-Comp. 52	>10	0.012	0.0077	0.004	0.022	0.0065
Tabla 3-Comp. 54	>10	0.086	0.041	0.017	0.111	0.094
Tabla 3-Comp. 58	7.65	0.044	0.049	0.014	0.108	0.034
Tabla 3-Comp. 91	8.409	0.298	0.129	0.033	0.72	0.084
Tabla 4-Comp. 5	>10	0.0007	0.0004	- - -	0.0022	0.0012

No. Tabla/ No. Comp.	Ba/F3 IC50 (μM)	Ba/F3 Tel-TrkA IC50 (μM)	Ba/F3 Tel-TrkB IC50 (μM)	Ba/F3 Tel-TrkC IC50 (μM)	Ba/F3 TRKA-NGF CTG IC50 (μM)	KM12 luc IC50 (μM)
Tabla 4-Comp. 14	5.716	0.021	0.0149	- - -	0.0452	0.0308
Tabla 4-Comp. 16	>10	0.0068	0.0015	- - -	0.0052	0.0022
Tabla 4-Comp. 25	7.502	0.010	0.0071	- - -	0.028	- - -
Tabla 4-Comp. 32	4.989	0.0014	0.0015	- - -	0.0026	- - -
Tabla 5-Comp. 1	7.658	0.051	0.038	0.021	0.043	0.0092
Tabla 5-Comp. 2	6.174	0.026	0.015	0.0084	0.049	0.029
Tabla 5-Comp. 4	5.36	0.166	0.060	0.032	0.203	0.089
Tabla 5-Comp. 13	4.837	0.0035	0.035	0.0017	0.0053	0.0075

A10

No. Tabla/ No. Comp.	Ba/F3 IC50 (μM)	Ba/F3 Tel-TrkA IC50 (μM)	Ba/F3 Tel-TrkB IC50 (μM)	Ba/F3 Tel-TrkC IC50 (μM)	Ba/F3 TRKA-NGF CTG IC50 (μM)	KM12 luc IC50 (μM)
Tabla 5-Comp. 17	>10	0.0064	0.015	0.0031	0.034	0.0088
Tabla 5-Comp. 22	2.249	0.132	0.088	0.027	0.316	0.099
Tabla 5-Comp. 23	3.713	0.136	0.074	0.016	0.111	0.109
Tabla 6-Comp. 1	4.129	1.63	1.175	0.334	1.496	1.377
Tabla 6-Comp. 3	>10	0.0015	0.0018	- - -	0.018	0.0072
Tabla 7-Comp. 1	>10	0.017	0.017	- - -	0.030	0.0076
Tabla 7-Comp. 2	>10	0.018	0.013	- - -	0.031	0.026
Tabla 7-Comp. 3	3.866	0.0069	0.0066	- - -	0.019	0.017

No. Tabla/ No. Comp.	Ba/F3 IC50 (μM)	Ba/F3 Tel-TrkA IC50 (μM)	Ba/F3 Tel-TrkB IC50 (μM)	Ba/F3 Tel-TrkC IC50 (μM)	Ba/F3 TRKA-NGF CTG IC50 (μM)	KM12 luc IC50 (μM)
Tabla 7-Comp. 5	4.82	0.0038	0.0062	- - -	0.0064	- - -
Tabla 7-Comp. 6	>10	0.023	0.039	- - -	0.062	- - -
Tabla 7-Comp. 8	1.57	0.0082	0.0088	- - -	0.0061	- - -
Tabla 7-Comp. 9	>10	0.059	0.063	- - -	0.053	0.014
Tabla 7-Comp. 10	>10	0.061	0.071	- - -	0.077	- - -
Tabla 7-Comp. 12	>10	0.0061	0.0067	- - -	0.0081	0.0012
Tabla 7-Comp. 17	>10	0.081	0.044	- - -	0.093	- - -
Tabla 7-Comp. 18	>10	0.047	0.0048	- - -	0.064	- - -

No. Tabla/ No. Comp.	Ba/F3 IC50 (μM)	Ba/F3 Tel-TrkA IC50 (μM)	Ba/F3 Tel-TrkB IC50 (μM)	Ba/F3 Tel-TrkC IC50 (μM)	Ba/F3 TRKA-NGF CTG IC50 (μM)	KM12 luc IC50 (μM)
Tabla 7-Comp. 20	>10	0.0018	0.0016	- - -	0.0036	- - -
Tabla 7-Comp. 21	>10	0.090	0.067	- - -	0.121	- - -
Tabla 7-Comp. 22	>10	0.043	0.023	- - -	0.035	- - -
Tabla 7-Comp. 26	>10	0.0077	0.0075	- - -	0.012	- - -
Tabla 7-Comp. 54	>10	0.028	0.037	- - -	0.041	- - -
Tabla 7-Comp. 57	6.895	0.020	0.020	- - -	0.020	- - -
Tabla 7-Comp. 58	>10	0.115	0.15	- - -	0.21	- - -
Tabla 7-Comp. 61	>10	0.0089	0.0079	- - -	0.0098	0.0040

No. Tabla/ No. Comp.	Ba/F3 IC50 (μM)	Ba/F3 Tel-TrkA IC50 (μM)	Ba/F3 Tel-TrkB IC50 (μM)	Ba/F3 Tel-TrkC IC50 (μM)	Ba/F3 TRKA-NGF CTG IC50 (μM)	KM12 luc IC50 (μM)
Tabla 7-Comp. 82	0.397	0.0089	0.010	- - -	0.00512	- - -
Tabla 7-Comp. 96	5.989	0.001	0.002		0.003	
Tabla 7-Comp. 98	>11	0.006	0.009		0.013	
Tabla 7-Comp. 100	4.378	0.002	0.002		0.003	
Tabla 7-Comp. 115	4.842	0.014	0.014		0.016	
Tabla 7-Comp. 116	>9.10	0.003	0.003		0.008	0.003
Tabla 7-Comp.	>11	0.003	0.003		0.004	0.002

No. Tabla/ No. Comp.	Ba/F3 IC50 (μM)	Ba/F3 Tel-TrkA IC50 (μM)	Ba/F3 Tel-TrkB IC50 (μM)	Ba/F3 Tel-TrkC IC50 (μM)	Ba/F3 TRKA-NGF CTG IC50 (μM)	KM12 luc IC50 (μM)
119						
Tabla 7-Comp. 121	>10	0.00334	0.00302	- - -	0.00488	- - -
Tabla 7-Comp. 132	>11	0.002	0.002		0.004	
Tabla 7-Comp. 136	4.324	0.013	0.024		0.039	
Tabla 7-Comp. 143	>11	0.034	0.053		0.031	
Tabla 7-Comp. 153	>11	0.346	0.244		0.698	
Tabla 7-	>11	0.065	0.052		0.087	0.019

No. Tabla/ No. Comp.	Ba/F3 IC50 (μM)	Ba/F3 Tel-TrkA IC50 (μM)	Ba/F3 Tel-TrkB IC50 (μM)	Ba/F3 Tel-TrkC IC50 (μM)	Ba/F3 TRKA-NGF CTG IC50 (μM)	KM12 luc IC50 (μM)
Comp. 158						
Tabla 7-Comp. 171	>11	0.224	0.129		0.238	
Tabla 7-Comp. 176	2.753	1.119	0.971		0.886	
Tabla 7-Comp. 181	>11	0.007	0.008		0.014	
Tabla 7-Comp. 185	>11	0.064	0.07		0.119	
Tabla 7-Comp. 191	>9.56	0.014	0.012		0.016	

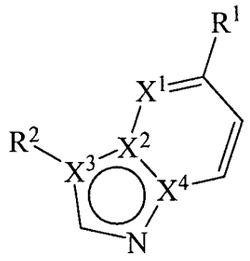
No. Tabla/ No. Comp.	Ba/F3 IC50 (μM)	Ba/F3 Tel-TrkA IC50 (μM)	Ba/F3 Tel-TrkB IC50 (μM)	Ba/F3 Tel-TrkC IC50 (μM)	Ba/F3 TRKA-NGF CTG IC50 (μM)	KM12 luc IC50 (μM)
Tabla 7-Comp. 201	>11	0.013	0.015		0.02	0.01
Tabla 7-Comp. 217	>11	0.027	0.03		0.06	
Tabla 7-Comp. 230	2.687	0.006	0.009		0.029	
Tabla 7-Comp. 231	>11	0.023	0.028		0.054	
Tabla 7-Comp. 238	>11	0.017	0.025		0.035	
Tabla 7-Comp.	6.385	0.144	0.147		0.13	

No. Tabla/ No. Comp.	Ba/F3 IC50 (μM)	Ba/F3 Tel-TrkA IC50 (μM)	Ba/F3 Tel-TrkB IC50 (μM)	Ba/F3 Tel-TrkC IC50 (μM)	Ba/F3 TRKA-NGF CTG IC50 (μM)	KM12 luc IC50 (μM)
249						
Tabla 7-Comp. 255	>11	0.009	0.017	0.003	0.009	0.006
Tabla 7-Comp. 257	>11	0.13	0.289		0.101	

Se entiende que los Ejemplos y modalidades descritas en la presente son para propósitos ilustrativos solamente, y que se sugerirán diferentes modificaciones o cambios a la luz de las mismas para las personas expertas en la técnica, y se deben incluir 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 la presente, se incorporan a la presente como referencia para todos los propósitos.

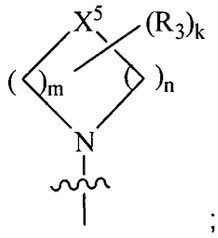
REIVINDICACIONES

1. Un compuesto de la fórmula (I), una sal farmacéuticamente aceptable, o un solvato farmacéuticamente aceptable del mismo:



Fórmula (I)

en donde:

R^1 es  ; en donde:

X^1, X^2, X^3 y X^4 son cada uno independientemente CR^9 o N, con la condición de que cuando menos uno de X^1, X^2 X^3 y X^4 es N, y cuando mucho solamente dos de X^1, X^2, X^3 y X^4 son N;

X^5 es $C(R^3)_2$, O, S, $S(O)_2$, S(O), o NR^3;

m es 1, 2, 3 ó 4;

n es 0, 1, 2 ó 3;

k es 0, 1, 2, 3, 4, 5 ó 6;

cada R^3 se selecciona independientemente a partir de

halógeno, nitro, $-N(R^4)_2$, $-OR^9$, -CN, =O, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-C(O)OR^9$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, $-OC(O)R^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, alquilo de 1 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono y heteroarilo de 2 a 13 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono y heteroarilo de 2 a 13 átomos de carbono de R^3 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, amino, nitro, hidroxilo, ciano, $-OR^9$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-C(O)OR^9$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, $-OC(O)R^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2$, alquilo de 1 a 8 átomos de carbono, amino-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono,

alquilo de 1 a 8 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno, cicloalquilo de 3 a 8 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, arilo de 6 a 14 átomos de carbono, y heteroarilo de 2 a 13 átomos de carbono;

de una manera alternativa, cada R^3 es independientemente un alquilo de 1 a 8 átomos de carbono, en donde cuando menos dos R^3 forman juntos un cicloalquilo de 3 a 8 átomos de carbono fusionado con un heterociclo, y en donde cada alquilo de 1 a 8 átomos de carbono de R^3 está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, amino, nitro, hidroxilo, ciano, $-OR^9$, alquilo de 1 a 8 átomos de carbono, amino-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno, cicloalquilo de 3 a 8 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, arilo de 6 a 14 átomos de carbono, y heteroarilo de 2 a 13 átomos de carbono;

R^2 es arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono o hetero-cicloalquilo de 2 a 14 átomos de carbono, en donde el arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono o hetero-cicloalquilo de 2 a 14 átomos de carbono de R^2 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de

halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-OC(O)R^9$, alcoxilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno y alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno;

cada R^4 se selecciona independientemente a partir de H, alquilo de 1 a 8 átomos de carbono, $-L^1R^5$, $-L^1R^6$, $-L^1R^8$, heteroarilo de 2 a 13 átomos de carbono, arilo de 6 a 14 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, y cicloalquilo de 3 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, y cicloalquilo de 3 a 8 átomos de carbono están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, deuterio, $-CD_3$, $-S(O)_2R^9$, -CN, alquilo de 1 a 8 átomos de carbono, $-OR^9$, $-N(R^9)_2$ y $-(CH_2)_pOR^9$;

L^1 es un enlace, alquileno de 1 a 8 átomos de carbono, alquenileno de 2 a 8 átomos de carbono, $-O(CH_2)_p-$, -C(O)-, $-N(R^9)-$, $(CH_2)_pC(O)-$, $-C(O)-(CH_2)_pO(CH_2)_p-$ o -C(O)O-;

Y^1 es arileno de 6 a 14 átomos de carbono, heteroarileno de 2 a 13 átomos de carbono, cicloalquileno de 3 a 8 átomos de carbono, hetero-cicloalquileno de 2 a 14 átomos de carbono, o

alcoxileno de 1 a 8 átomos de carbono, cada uno de los cuales está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, -C(O) OR^9, - $N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2$ $N(R^4)_2$, $-NR^4S(O)_2R^4$, $-OC(O)R^9$, alcoxilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, y alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno;

R^5 es arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, $-N(R^9)_2$, $-N(R^9)C(O)R^9$, $-C(O)N(R^9)_2$, $-(CH_2)_pOR^9$ u $-OR^9$.

R^6 es arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, $-OCH(R^7)_2$, $-OCH(R^7)_2$, $-C(O)R^7$, alquilo de 1 a 8 átomos de carbono, o cicloalquilo de 3 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, y hetero-cicloalquilo de 2 a 14 átomos de carbono de R^6 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, $-CN$, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^8$, $OC(O)N(R^4)_2$, $-N(R^9)_2$, $-C(O)C(O)OR^9$,

$-(CH_2)_pN(R^9)_2$, $-N(R^4)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-(CH_2)_pS(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-NR^4S(O)_2R^9$, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, alqueno de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por hidroxilo, alquilo de 1 a 8 átomos de carbono sustituido por halógeno y alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno;

o R^6 es arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono o cicloalquilo de 3 a 8 átomos de carbono que tiene un puente de alquilo de 1 a 4 átomos de carbono;

o R^6 es un hetero-cicloalquilo de 2 a 14 átomos de carbono opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados a partir de halógeno, =O, -CN, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-C(O)R^8$, $OC(O)N(R^4)_2$, $-N(R^9)_2$, $-C(O)C(O)OR^9$, $-(CH_2)_pN(R^9)_2$, $-N(R^4)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-(CH_2)_pS(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-NR^4S(O)_2R^9$, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, alqueno de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por hidroxilo, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, y alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno;

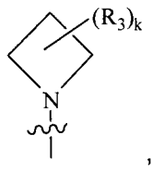
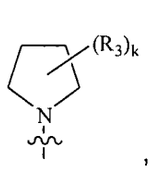
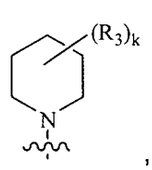
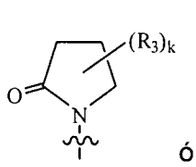
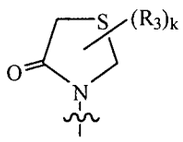
cada R^7 se selecciona independientemente a partir de H, alquilo de 1 a 8 átomos de carbono y $-L^1R^8$;

R^8 es H, $-N(R^9)_2$, $-N(R^4)_2$, $-SR^9$, -CN, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono y hetero-cicloalquilo de 2 a 14 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono y hetero-cicloalquilo de 2 a 14 átomos de carbono de R^8 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, alquilo de 1 a 6 átomos de carbono, $-CN$, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-C(O)R^9$, $-OC(O)R^9$, $-C(O)OR^9$, $-N(R^9)_2$, $-N(R^4)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)R^4$, $-N(R^4)C(O)OR^4$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, y $-NR^4S(O)_2$;

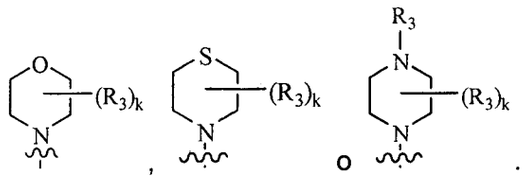
cada R^9 se selecciona independientemente a partir de H, cicloalquilo de 3 a 8 átomos de carbono y alquilo de 1 a 8 átomos de carbono, y

cada p es independientemente 1, 2, 3, 4, 5 ó 6.

2. El compuesto de la reivindicación 1, en donde:

R^1 es  ,  ,  ,  ó  .

3. El compuesto de la reivindicación 1, en donde:

R^1 es  .

4. El compuesto de cualquiera de las reivindicaciones 1 a 3, en donde cada R^3 se selecciona independientemente a partir de halógeno, $-OR^9$, alquilo de 1 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono y heteroarilo de 2 a 13 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono y heteroarilo de 2 a 13 átomos de carbono de R^3 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hidroxilo, $-OR^9$, alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno y cicloalquilo de 3 a 8 átomos de carbono.

5. El compuesto de cualquiera de las reivindicaciones 1 a 4, en donde el arilo de 6 a 14 átomos de carbono de R^3 es fenilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, alquilo de 1 a 8 átomos de

carbono, y alquilo de 1 a 8 átomos de carbono sustituido por halógeno.

6. El compuesto de cualquiera de las reivindicaciones 1 a 5, en donde el arilo de 6 a 14 átomos de carbono de R^3 es fenilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de flúor y alquilo de 1 a 8 átomos de carbono.

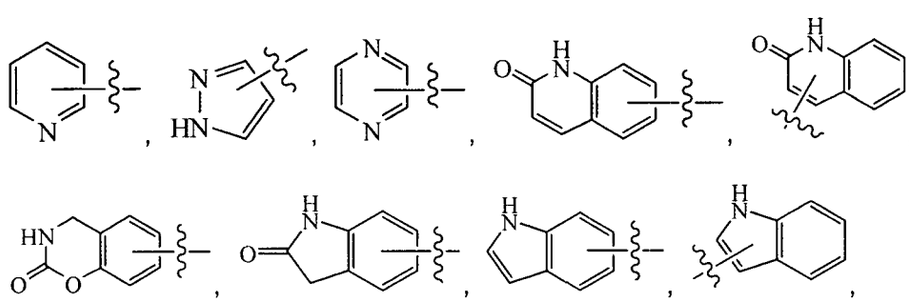
7. El compuesto de cualquiera de las reivindicaciones 1 a 6, en donde R^2 es arilo de 6 a 14 átomos de carbono, o heteroarilo de 2 a 13 átomos de carbono, en donde el arilo de 6 a 14 átomos de carbono, y heteroarilo de 2 a 13 átomos de carbono de R^2 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$, $-S(O)_2R^9$, $-S(O)_2N(R^4)_2$, $-NR^4S(O)_2R^4$, $-OC(O)R^9$, alcoxilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono sustituido por halógeno y alcoxilo de 1 a 8 átomos de carbono sustituido por halógeno.

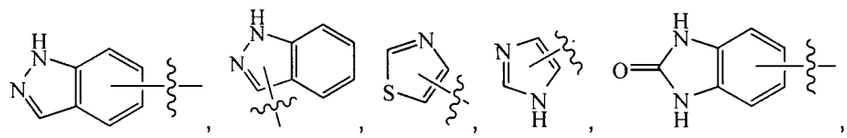
8. El compuesto de cualquiera de las reivindicaciones 1 a 7, en donde R^2 es arilo de 6 a 14 átomos de carbono, o heteroarilo de 2 a 13 átomos de carbono, en donde el arilo de 6 a 14 átomos de carbono, y heteroarilo de 2 a 13 átomos de carbono de R^2 están

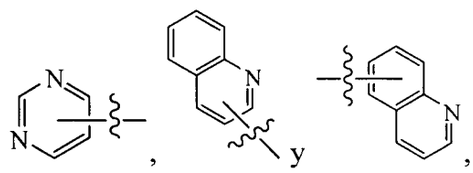
opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ y $-S(O)_2R^9$.

9. El compuesto de cualquiera de las reivindicaciones 1 a 8, en donde el arilo de 6 a 14 átomos de carbono de R^2 es fenilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ y $-S(O)_2R^9$.

10. El compuesto de cualquiera de las reivindicaciones 1 a 8, en donde el heteroarilo de 2 a 13 átomos de carbono de R^2 se selecciona a partir de:

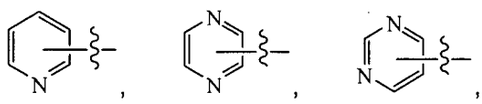






en donde cada uno está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ y $-S(O)_2R^9$.

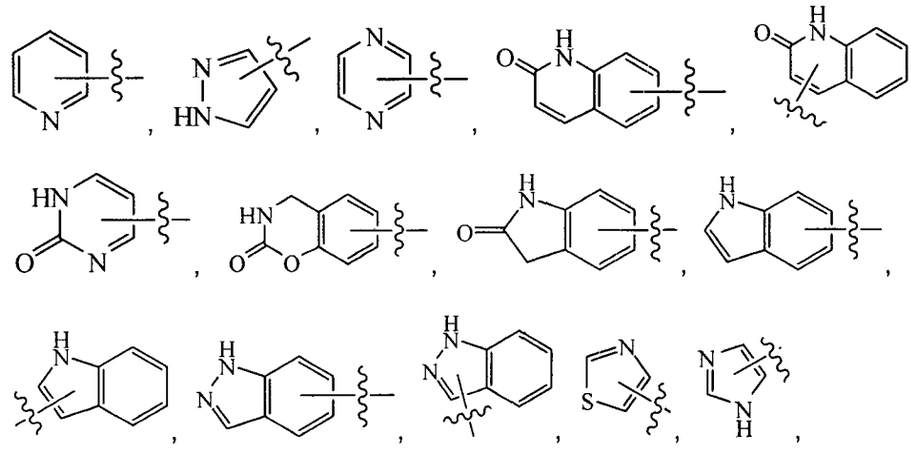
11. El compuesto de cualquiera de las reivindicaciones 1 a 8, en donde el heteroarilo de 2 a 13 átomos de carbono de cada R^2 se selecciona a partir de:

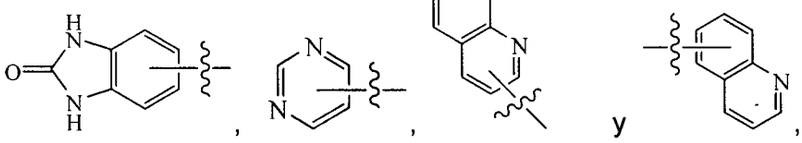


en donde cada uno está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, -CN, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-C(O)R^9$, $-OR^9$, $-C(O)OR^9$, $-N(R^4)_2$, $-R^6$, $-OR^6$, $-L^1R^5$, $-L^1R^6$, $-Y^1R^5$, $-Y^1R^6$ y $-S(O)_2R^9$.

12. El compuesto de cualquiera de las reivindicaciones 1 a 11, en donde R^6 es heteroarilo de 2 a 13 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, -OCH $(R^7)_2$, alquilo de 1 a 8 átomos de carbono, o cicloalquilo de 3 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, y hetero-cicloalquilo de 2 a 14 átomos de carbono de R^6 están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, –CN, $–OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)\ OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-N(R^4)_2$, $–S(O)_2R^9$, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, alqueno de 2 a 8 átomos de carbono, y alquilo de 1 a 8 átomos de carbono sustituido por hidroxilo.

13. El compuesto de cualquiera de las reivindicaciones 1 a 12, en donde R^6 se selecciona a partir de:

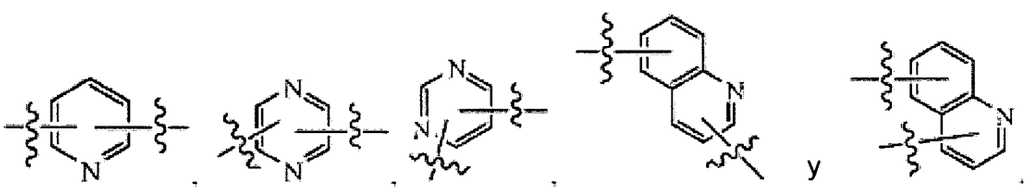




en donde cada uno está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente a partir de halógeno, –CN, $-OR^9$, $-(CH_2)_pOR^9$, $-L^1C(O)R^8$, $-L^1R^8$, $-L^1R^5$, $-C(O)OR^9$, $-C(O)R^9$, $-N(R^9)_2$, $-C(O)N(R^4)_2$, $-N(R^4)C(O)OR^4$, $-N(R^4)C(O)R^4$, $-N(R^4)_2$, $-S(O)_2R^9$, hetero-cicloalquilo de 2 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, alquilo de 1 a 8 átomos de carbono, alqueno de 2 a 8 átomos de carbono, y alquilo de 1 a 8 átomos de carbono sustituido por hidroxilo.

14. El compuesto de cualquiera de las reivindicaciones 1 a 13, en donde Y^1 es arileno de 6 a 14 átomos de carbono o heteroarileno de 2 a 13 átomos de carbono

15. El compuesto de cualquiera de las reivindicaciones 1 a 14, en donde Y^1 se selecciona a partir de:



16. El compuesto de cualquiera de las reivindicaciones 1 a 15, en donde cada R^4 se selecciona independientemente a partir de H, alquilo de 1 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, $-L^1R^5$, $-L^1R^6$ y cicloalquilo de 3 a 8 átomos de carbono, en donde el alquilo

de 1 a 8 átomos de carbono, arilo de 6 a 14 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, y cicloalquilo de 3 a 8 átomos de carbono están opcionalmente sustituidos con -$(CH_2)_pOR^9$.

17. El compuesto de cualquiera de las reivindicaciones 1 a 16, R^5 es arilo de 6 a 14 átomos de carbono, heteroarilo de 2 a 13 átomos de carbono, hetero-cicloalquilo de 2 a 14 átomos de carbono, $-N(R^9)_2$, $-N(R^9)C(O)R^9$, $-(CH_2)_pOR^9$, u $-OR^9$.

18. El compuesto de cualquiera de las reivindicaciones 1 a 17, R^7 es $-L^1R^8$.

19. El compuesto de cualquiera de las reivindicaciones 1 a 18, R^8 es $-N(R^9)_2$ o -CN.

20. El compuesto de la reivindicación 1 seleccionado a partir de:

(R)-1-(4-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-pirrolidin-3-ol;

(R)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-piperidin-4-ol;

6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-indolin-2-ona;

3-(6-((3S)-2-(3-fluoro-fenil)-3-hidroxi-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

5-(6-(2-(2,5-dimetil-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-fluoro-benzonitrilo;

(R)-4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

4-(5-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-morfolina;

4-(5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-morfolina;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-N-metil-picolinamida;

4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

5-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-N-metil-picolinamida;

(S)-4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

(R)-4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

4-(5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-morfolina;

4-(6-(2-fenil-azetidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

(R)-4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

(S)-4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-

b]-piridazin-3-il)-benzonitrilo;

4-(6-(2-(3-fluoro-fenil)-2-metil-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-3,4-dihidro-2H-benzo-[e][1,3]-oxazin-2-ona;

6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-3,4-dihidro-2H-benzo-[e][1,3]-oxazin-2-ona;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-indolin-2-ona;

6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-indolin-2-ona;

4-(6-(2-(2,5-difluoro-fenil)-5-metil-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

4-(2-(4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-1H-pirazol-1-il)-etil)-morfolina;

N-(2-(4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-1H-pirazol-1-il)-etil)-acetamida;

(Z)-3-((1H-pirrol-2-il)-metilen)-6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-indolin-2-ona;

5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-fluoro-benzonitrilo;

5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-morfolino-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-fluoro-benzonitrilo;

5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(dimetil-amino)-benzonitrilo;

5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-metil-piperazin-1-il)-benzonitrilo;

5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-(2-metoxi-etil)-piperazin-1-il)-benzonitrilo;

5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-morfolino-etil-amino)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(dimetil-amino)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-metil-piperazin-1-il)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-(2-metoxi-etil)-piperazin-1-il)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-morfolino-etil-amino)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-morfolino-benzonitrilo;

3-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-morfolino-piperidin-1-il)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(pirrolidin-1-il)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-

piridazin-3-il)-2-(3-(dimetil-amino)-pirrolidin-1-il)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2,6-dimetil-morfolino)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-(pirrolidin-1-il)-etoxi)-benzonitrilo;

5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-nicotinonitrilo;

6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-picolinonitrilo;

4-(4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-tiazol-2-il)-morfolina;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(3-morfolino-propil-amino)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(3-morfolino-pirrolidin-1-il)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(1-metil-pirrolidin-3-iloxi)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-((2-(dimetil-amino)-etil)-(metil)-amino)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-((l-metil-pirrolidin-3-il)-metoxi)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(3-morfolino-propoxi)-benzonitrilo;

3-(5-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo;

4-(5-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo;

3-(5-(2-(2,5-difluoro-fenil)-tiazolidin-3-il)-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo;

3-(5-(2-(2,5-difluoro-fenil)-tiazolidin-3-il)-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo;

3-(3-(1H-imidazol-2-il)-fenil)-5-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3H-imidazo-[4,5-b]-piridina;

3-(5-(2-(2,5-difluoro-fenil)-4-oxo-tiazolidin-3-il)-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo;

3-(5-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo;

4-(5-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3H-imidazo-[4,5-b]-piridin-3-il)-benzonitrilo;

3-(6-(2-(3-fluoro-fenil)-3-oxo-pirazolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

5-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-hidroxi-piperidin-1-il)-benzonitrilo;

2-(1,3-bis-(dimetil-amino)-propan-2-iloxi)-4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(1-(dimetil-amino)-propan-2-iloxi)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-(1-metil-pirrolidin-2-il)-etoxi)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(3-(dimetil-amino)-2-hidroxi-propoxi)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-((1-metil-pirrolidin-2-il)-metoxi)-benzonitrilo;

4-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

3-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

2-(2-(dietil-amino)-etil-amino)-4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

7-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-oxo-1,2-dihidro-quinolin-3-carbonitrilo;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-morfolino-benzonitrilo;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-metil-piperazin-1-il)-benzonitrilo;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-(2-metoxi-etil)-piperazin-1-il)-benzonitrilo;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-morfolino-etil-amino)-benzonitrilo;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-morfolino-piperidin-1-il)-benzonitrilo;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-(pirrolidin-1-il)-etoxi)-benzonitrilo;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-

piridazin-3-il)-2-(2-(1-metil-pirrolidin-2-il)-etoxi)-benzonitrilo;

4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-metil-piperazin-1-il)-benzonitrilo;

4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-(pirrolidin-1-il)-etoxi)-benzonitrilo;

4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-morfolino-etoxi)-benzonitrilo;

(R)-3-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

(S)-3-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

4-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

(R)-4-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

(S)-4-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

ácido 6-(6-(2-(2,5-dimetil-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-picolínico;

3-(6-((2R,4S)-3,3-difluoro-4-metil-2-fenil-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

3-(6-(2-fenil-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo; 6-(6-(2-fenil-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-3,4-dihidro-2H-benzo-[e][1,3]-oxazin-2-ona;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-

piridazin-3-il)-2-((R)-pirrolidin-2-il-metoxi)-benzonitrilo;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-((S)-pirrolidin-2-il-metoxi)-benzonitrilo;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-(2-morfolino-2-oxo-etil)-piperazin-1-il)-benzonitrilo;

2-(4-(2-ciano-4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-fenil)-piperazin-1-il)-N,N-dimetil-acetamida;

2-(4-(3-(dimetil-amino)-propil)-piperazin-1-il)-5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-hidroxi-piperidin-1-il)-benzonitrilo;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-(4-isopropil-piperazin-1-il)-etoxi)-benzonitrilo;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(2-(4-(2-hidroxi-etil)-piperazin-1-il)-etoxi)-benzonitrilo;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(((R)-5-oxo-pirrolidin-2-il)-metoxi)-benzonitrilo;

3-(6-((2R,4S)-3,3-difluoro-2-(3-fluoro-fenil)-4-metil-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(1H-indol-4-il)-imidazo-[1,2-b]-piridazina;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(1-metil-1H-indol-2-

il)-imidazo-[1,2-b]-piridazina;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(1H-indol-5-il)-imidazo-[1,2-b]-piridazina;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(5-(4-metil-piperazin-1-il)-pirazin-2-il)-imidazo-[1,2-b]-piridazina;

4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(piperidin-1-il)-tiazol;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(5-(pirrolidin-1-il)-pirazin-2-il)-imidazo-[1,2-b]-piridazina;

4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-carboxilato de terbutilo;

3-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-metil-fenil-carbamato de terbutilo;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(piridin-2-il)-imidazo-[1,2-b]-piridazina;

3-(6-cloro-pirazin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina;

3-(6-(1H-imidazol-1-il)-pirazin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina;

2-cloro-5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-tiazol;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-N,N-dimetil-pirazin-2-amina;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-morfolina;

(S)-6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-picolinonitrilo;

(R)-6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-picolinonitrilo;

3-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-indolin-2-ona;

6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(1H-indol-4-il)-imidazo-[1,2-b]-piridazina;

4-(6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-morfolina;

6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(1H-indol-5-il)-imidazo-[1,2-b]-piridazina;

(R)-4-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

(S)-4-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(1H-indazol-5-il)-imidazo-[1,2-b]-piridazina;

3-(5-fluoro-6-metil-piridin-2-il)-6-(2-(3-fluoro-fenil)-

pirrolidin-1-il)-imidazo-[1,2-b]-piridazina;

3-(3-fluoro-fenil)-4-(3-(piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina;

6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-nicotinonitrilo;

2-fluoro-5-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-metoxi-piridin-2-il)-imidazo-[1,2-b]-piridazina;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-fluoro-piridin-2-il)-imidazo-[1,2-b]-piridazina;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-N-(2-hidroxi-etil)-picolinamida;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-picolinamida;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(1H-indazol-6-il)-imidazo-[1,2-b]-piridazina;

6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(1H-indazol-6-il)-imidazo-[1,2-b]-piridazina;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(piperazin-1-il)-piridin-3-il)-imidazo-[1,2-b]-piridazina;

2-(4-(2-ciano-4-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-fenil)-piperazin-1-il)-N,N-dimetil-acetamida;

2-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il-amino)-etanol;

1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol;

6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(6-fluoro-piridin-2-il)-imidazo-[1,2-b]-piridazina;

4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-2-ona;

7-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-oxo-1,2-dihidro-quinolin-3-carbonitrilo;

4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(piperazin-1-il-metil)-benzonitrilo;

N1,N1-dietil-N2-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-etan-1,2-diamina;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(4-metil-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

(2S)-3-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il-amino)-propano-1,2-diol;

6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(6-(piperazin-1-il)-piridin-3-il)-imidazo-[1,2-b]-piridazina;

6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(6-(piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-3-(6-(4-metil-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

4-(6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-2-ona;

(3S)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-

[1,2-b]-piridazin-3-il)-piridin-2-il)-pirrolidin-3-ol;

(3R)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirrolidin-3-ol;

(3S,4S)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirrolidin-3,4-diol;

3-(3-fluoro-fenil)-4-(3-(5-(morfolino-metil)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina;

4-((6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-3-il)-metil)-morfolina;

4-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-2-((4-metil-piperazin-1-il)-metil)-benzonitrilo;

1-(6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol;

3-(3-fluoro-fenil)-4-(3-(6-fluoro-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina;

(5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-(4-hidroxi-piperidin-1-il)-metanona;

3-(3-fluoro-fenil)-4-(3-(6-morfolino-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina;

3-(3-fluoro-fenil)-4-(3-(6-(piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina;

4-(6-(2-(2-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

3-(6-(2-(2-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

4-(4-(6-(2-(2-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-tiazol-2-il)-morfolina;

5-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-metil-piperazin-1-il)-benzonitrilo;

2-(4-acetil-piperazin-1-il)-5-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-benzonitrilo;

5-(6-(2-(2-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(4-hidroxi-piperidin-1-il)-benzonitrilo;

1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol;

N-(5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-pirazin-2-il)-ciclopropan-carboxamida;

4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-((4-metil-piperazin-1-il)-metil)-benzonitrilo;

(2S)-4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-2-metil-morfolina;

ácido 1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carboxílico;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-metoxi-tiazol;

ácido 4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-tiazol-2-carboxílico;

(4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-tiazol-2-il)-metanol;

1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-

piridazin-3-il)-piridin-2-il)-piperidin-3-ol;

(3R)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N,N-dimetil-pirrolidin-3-amina;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(1-metil-1H-imidazol-2-il)-imidazo-[1,2-b]-piridazina;

5-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-2-(piperazin-1-il)-benzonitrilo;

4-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-carboxilato de terbutilo;

3-(3-fluoro-fenil)-4-(3-(6-(4-metil-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina;

4-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-2,6-dimetil-morfolina;

3-(3-fluoro-fenil)-4-(3-(6-(piperidin-4-iloxi)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina;

4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-(piperazin-1-il-metil)-tiazol;

2,2'-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il-azan-di-il)-dietanol;

4-(2-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-iloxi)-etil)-morfolina;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(2-(pirrolidin-1-il)-etoxi)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

4-((6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-metil)-morfolina;

4-((6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-metil)-2,6-dimetil-morfolina;

1-((6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-metil)-pirrolidin-3-ol;

4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2-metoxi-tiazol;

4-(5-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-2-oxo-2,3-dihidro-1H-benzo-[d]-imidazol-1-il)-piperidin-1-carboxilato de etilo;

6-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-nicotinonitrilo;

5-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-1-(piperidin-4-il)-1H-benzo-[d]-imidazol-2(3H)-ona;

2-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-N,N-dimetil-acetamida;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(4-isopropil-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

2-(1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-il)-propan-2-ol;

4-(1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-il)-morfolina;

3-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-propano-nitrilo;

1-(6-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol;

2-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-N-isopropil-acetamida;

(1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-il)-metanol;

(1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-3-il)-metanol;

1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carbonitrilo;

2-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-etanol;

(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-metanol;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(5-metil-1H-imidazol-2-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-picolinamida;

(R)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-fluoro-piridin-2-il)-imidazo-[1,2-b]-piridazina;

(R)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol;

(1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-il)-metanol;

2-(1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-il)-etanol;

1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-

piridazin-3-il)-piridin-2-il)-piperidin-3-carboxamida;

1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carboxamida;

6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-ol;

ácido 6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-picolínico;

2-fluoro-3-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-quinolina;

3-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-quinolin-2(1H)-ona;

5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-quinolina;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(4-(metil-sulfonil)-fenil)-imidazo-[1,2-b]-piridazina;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(piperidin-4-iloxi)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

(1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il-amino)-ciclopentil)-metanol;

3-(3-fluoro-fenil)-4-(3-(6-(4-(1-metil-piperidin-4-il)-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina;

3-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-quinolina;

(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-(4-hidroxi-piperidin-1-il)-metanona;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(2-fluoro-piridin-4-il)-imidazo-[1,2-b]-piridazina;

1-(4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol;

N1,N1-dietil-N2-(6-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-etan-1,2-diamina;

6-(2-(3-fluoro-fenil)-piperidin-1-il)-3-(6-(4-isopropil-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

(3S)-1-(6-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N,N-dimetil-pirrolidin-3-amina;

4-(3-(6-(2,5-diazabiciclo-[2.2.1]-heptan-2-il)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-3-(3-fluoro-fenil)-morfolina;

6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-N-(2-(piperazin-1-il)-etil)-piridin-2-amina;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(1-(metil-sulfonil)-piperidin-4-iloxi)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-a]-piridin-3-il)-2-fluoro-benzonitrilo;

2-etoxi-4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-a]-piridin-3-il)-tiazol;

5-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-a]-piridin-3-il)-2-fluoro-benzonitrilo;

ácido 4-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-picolínico;

ácido 5-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-

b]-piridazin-3-il)-picolínico;

(2S,6R)-4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-2,6-dimetil-morfolina;

4-(6-(6-(2-(piridin-2-il)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-morfolina;

1-(6-(6-(2-(piridin-2-il)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol;

1-(6-(6-(2-(piridin-3-il)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol;

6-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-N-metil-piridin-2-amina;

6-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-N-isopropil-piridin-2-amina;

N-(6-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-metan-sulfonamida;

6-(6-(2-(3-fluoro-fenil)-piperidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-N,N-dimetil-piridin-2-amina;

6-(2-(3-fluoro-fenil)-piperidin-1-il)-3-(6-(piperidin-4-iloxi)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

ácido 1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-azetidin-3-carboxílico;

1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-azetidin-3-ol;

4-(6-(2-(2,5-difluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-a]-piridin-3-il)-2-etoxi-tiazol;

1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol;

(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-metanol;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(5-metil-1H-imidazol-2-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

(1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-il)-metanol;

2-(4-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-etanol;

1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-3-carboxamida;

1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carboxamida;

3-(3-fluoro-fenil)-4-(3-(6-(4-(1-metil-piperidin-4-il)-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina;

4-(3-(6-(2,5-diazabiciclo-[2.2.1]-heptan-2-il)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-3-(3-fluoro-fenil)-morfolina;

6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-N-(2-(piperazin-1-il)-etil)-piridin-2-amina;

1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N-metil-piperidin-4-carboxamida;

1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N-(2-hidroxi-etil)-piperidin-4-carboxamida;

(S)-6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-

piridazin-3-il)-indolin-2-ona;

(R)-6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-indolin-2-ona;

(S)-1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol;

(R)-1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-ol;

1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carboxilato de etilo;

3-(6-(1,3-dioxolan-2-il)-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina;

ácido 1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carboxílico;

5-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-oxazol;

3-(3-fluoro-fenil)-4-(3-(6-(4-(3-isopropil-1,2,4-oxadiazol-5-il)-piperidin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il)-morfolina;

N-(ciclopropil-metoxi)-1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carboxamida;

1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N-isopropil-piperidin-4-carboxamida;

N-ciclopropil-1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carboxamida;

1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-

piridazin-3-il)-piridin-2-il)-N-(isoxazol-3-il)-piperidin-4-carboxamida;

(1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-il)-(3-hidroxi-pirrolidin-1-il)-metanona;

N-(ciano-metil)-1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-carboxamida;

2-(1-(6-(6-(3-(3-fluoro-fenil)-morfolino)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperidin-4-il)-etanol;

3-(6-(1H-pirazol-5-il)-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina;

5-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirazolo-[1,5-a]-pirimidin-2-carbonitrilo;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(2-metil-pirimidin-4-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-amina;

3-(6-((2R,5S)-2,5-dimetil-piperazin-1-il)-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina;

3-(6-((3S,5R)-3,5-dimetil-piperazin-1-il)-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina;

6-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2(1H)-ona;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(4-(pirazin-2-il)-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(4-(pirimidin-2-il)-

piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(3-(piperidin-4-il)-1H-pirazol-5-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

4-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-morfolina;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(4-(2-(metil-sulfonil)-etil)-piperazin-1-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

2-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il-amino)-etanol;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(6-(piperidin-4-il)-pirimidin-4-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

2-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-N,N-dimetil-etanamina;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(pirimidin-4-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

4-(1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirrolidin-3-il)-morfolina;

3-(6-(4-(ciclopropil-sulfonil)-piperazin-1-il)-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina;

1-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-2-hidroxi-etanona;

(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-(1-hidroxi-ciclopropil)-metanona;

(R)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(2-metil-

pirimidin-4-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-(tetrahidro-2H-piran-4-il)-metanona;

(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-piperazin-1-il)-(tetrahidrofuran-2-il)-metanona;

4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,3'-bipiridin-6'-il)-morfolina;

6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(5-(pirrolidin-1-il)-pirazin-2-il)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

4-(5-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-morfolina;

1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-piperidin-4-ol;

N1-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-N2,N2-dimetil-etan-1,2-diamina;

1-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-piperidin-4-ol;

4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N,N-dimetil-pirimidin-2-amina;

3-(6-(1H-indazol-5-il)-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina;

2-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-

piridazin-3-il)-2,3'-bipiridin-6'-il-amino)-etanol;

1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,3'-bipiridin-6'-il)-piperidin-4-ol;

(R)-2-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il-amino)-etanol;

4-((S)-1-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirrolidin-3-il)-morfolina;

(2S,6R)-4-((S)-1-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirrolidin-3-il)-2,6-dimetil-morfolina;

(R)-1-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-azetidin-3-ol;

(R)-N-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-metan-sulfonamida;

(R)-4-((S)-1-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirrolidin-3-il)-2-metil-morfolina;

(R)-2-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il-amino)-etanol;

(R)-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-azetidin-3-ol;

(R)-1-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-pirrolidin-3-ol;

(R)-N-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-metan-sulfonamida;

(R)-4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N-(piridin-3-il-metil)-pirimidin-2-amina;

(S)-1-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-N-metil-pirrolidin-3-amina;

(R)-4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N-(2-(metil-sulfonil)-etil)-pirimidin-2-amina;

(R)-N-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,3'-bipiridin-6'-il)-metan-sulfonamida;

(R)-3-(6-(1H-indazol-6-il)-piridin-2-il)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazina;

(R)-1-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-N-metil-pirrolidin-3-amina;

(R)-1-(6'-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,2'-bipiridin-6-il)-piperidin-4-ol;

(R)-2-(6'-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,2'-bipiridin-6-il-amino)-etanol;

(R)-1-(6'-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,2'-bipiridin-6-il)-N-metil-pirrolidin-3-amina;

(R)-1-(4-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-N-metil-pirrolidin-3-amina;

(R)-2-(4-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-pirimidin-2-il)-piperazin-1-il)-etanol;

(R)-2-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-

[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-piperazin-1-il)-etanol;

1-((2S,6R)-4-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-2,6-dimetil-piperazin-1-il)-2-hidroxi-etanona;

(R)-1-(6'-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,2'-bipiridin-6-il)-pirrolidin-3-ol;

(R)-2-(4-(6'-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,2'-bipiridin-6-il)-piperazin-1-il)-etanol;

(R)-4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-bencen-sulfonamida;

(R)-3-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-bencen-sulfonamida;

(R)-N-(6'-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,2'-bipiridin-6-il)-metan-sulfonamida;

(R)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(2'-(piperazin-1-il)-2,4'-bipiridin-6-il)-imidazo-[1,2-b]-piridazina;

(R)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(6-(4-(metil-sulfonil)-fenil)-piridin-2-il)-imidazo-[1,2-b]-piridazina;

(R)-4-(2-(4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-1H-pirazol-1-il)-etil)-morfolina;

(R)-6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-3-(2'-(4-isopropil-piperazin-1-il)-2,4'-bipiridin-6-il)-imidazo-[1,2-b]-piridazina;

(R)-4-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-piridin-2-il)-N-metil-bencen-sulfonamida;

(S)-1-(6-(6-((R)-2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-pirrolidin-3-ol;

2-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-(piperidin-4-iloxi)-piridina;

{1-[(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-amino]-ciclopentil}-metanol;

(3S,4S)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3,4-diol;

1-{6-[6-(3-fenil-tiomorfolin-4-il)-imidazo-[1,2-b]-piridazin-3-il]-piridin-2-il}-piperidin-4-ol;

2-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-[(1-metan-sulfonil-piperidin-4-il)-oxi]-piridina;

(3S,4S)-1-(6-{6-[(2S)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3,4-diol;

(3S,4S)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3,4-diol;

4-(4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-1H-pirazol-1-il)-piperidina;

N-[(3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-N-metil-metan-sulfonamida;

2-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-(3-fluoro-piperidin-1-il)-piridina;

N-[(3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-N-metil-acetamida;

N-[(3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-2-hidroxi-N-metil-acetamida;

2-(3,3-difluoro-piperidin-1-il)-6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridina;

N-etil-N-[(3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-acetamida;

N-etil-N-[(3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-2-hidroxi-acetamida;

N-[(3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-metan-sulfonamida;

N-[1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-il]-N-metil-metan-sulfonamida;

N-[1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-il]-acetamida;

1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-3-metil-piperidin-4-ol;

1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-amina;

2,2,2-trifluoro-N-[(3S)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-acetamida;

N-[(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-

imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-metan-sulfonamida;

N-etil-N-[(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-acetamida;

N-[1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-il]-N-metil-metan-sulfonamida;

(3S)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-amina;

2-(dimetil-amino)-1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-etan-1-ona;

(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-3-metil-piperazina;

acetato de 2-[(2R)-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-2-metil-piperazin-1-il]-2-oxoetilo;

1-[(2R)-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-2-metil-piperazin-1-il]-2-hidroxi-etan-1-ona;

2-amino-1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-etan-1-ona;

1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-2-(metil-amino)-etan-1-ona;

2-(dimetil-amino)-1-[(2R)-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-2-metil-piperazin-1-il]-etan-1-ona;

(3R)-3-{[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-carbonil}-morfolina;

(3R)-3-{[(2R)-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-2-metil-piperazin-1-il]-carbonil}-morfolina;

8-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-octahidro-piperazino-[2,1-c]-morfolin-4-ona;

(3R,4R)-1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piridin-2-il]-pirrolidin-3,4-diol;

1-(6-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-ol;

6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-carboxamida;

6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-ol;

ácido 6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-carboxílico;

2-fluoro-3-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-quinolina;

3-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-1,2-dihidro-quinolin-2-ona;

5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-quinolina;

2-(3-fluoro-fenil)-1-[3-(4-metan-sulfonil-fenil)-imidazo-[1,2-b]-piridazin-6-il]-pirrolidina;

3-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-quinolina;

1-[(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-carbonil]-piperidin-4-ol;

2-fluoro-4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridina;

1-(4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-ol;

1-(4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-metil-piperazina;

2-[(4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-amino]-etan-1-ol;

(3R)-1-[(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-carbonil]-N,N-dimetil-pirrolidin-3-amina;

1-(5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirimidin-2-il)-piperidin-4-ol;

6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-N-metil-piridin-2-carboxamida;

4-[(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-carbonil]-morfolina;

(3R)-1-(4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-ol;

(3S)-1-(4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-ol;

(3R,4R)-1-(4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3,4-diol;

1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N,N-dimetil-piperidin-4-amina;

2-[(5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirimidin-2-il)-amino]-etan-1-ol;

5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-N-metil-pirimidin-2-amina;

5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-N,N-dimetil-pirimidin-2-amina;

1-(4-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N,N-dimetil-piperidin-4-amina;

2-cloro-5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirimidina;

4-[(5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirimidin-2-il)-oxi]-piperidin-1-carboxilato de terbutilo;

5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-2-(piperidin-4-iloxi)-pirimidina;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-

[1,2-b]-piridazin-3-il}-piridin-2-il)-N,N-dimetil-piperidin-4-amina;

5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirimidina;

5-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-1,2-dihidro-pirimidina;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-ona;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazina;

6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-N-[1-(propan-2-il)-piperidin-4-il]-piridin-2-amina;

carbamato de [1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-il];

N-metil-carbamato de 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-ilo;

N-terbutil-carbamato de 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-ilo;

1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-etan-1-ona;

N,N-dietil-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-amina;

2,2,2-trifluoro-1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-etan-1-

ona;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-metan-sulfonil-piperazina;

2-(benciloxi)-1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-etan-1-ona;

1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-2-hidroxi-etan-1-ona;

2-{[1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-il]-amino}etan-1-ol;

2-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-(1,2,3,6-tetrahidro-piridin-1-il)-piridina;

N,N-dietil-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-amina;

N-ciclopropil-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-amina;

(3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-metil-pirrolidin-3-amina;

(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-metil-pirrolidin-3-amina;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-metil-piperidin-4-amina;

2-fluoro-N-[1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-N,2-dimetil-propanamida;

2-fluoro-N-[1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-N-metil-propanamida;

1-terbutil-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazina;

ácido 1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-carboxílico;

2-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-[4-(pirrolidin-1-il)-piperidin-1-il]-piridina;

2-fluoro-N-[1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-il]-N,2-dimetil-propanamida;

2,2,2-trifluoro-N-[(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-N-metil-acetamida;

6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-N-metil-N-(piperidin-4-il)-piridin-2-amina;

2-fluoro-N-[(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-N,2-dimetil-propanamida;

[1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-il]-metanol;

(3R)-N-(2-fluoro-2-metil-propil)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-metil-pirrolidin-3-amina;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-(propan-2-sulfonil)-piperazina;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-[(2-metil-propan)-sulfonil]-piperazina;

1-(butan-2-sulfonil)-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazina;

1-(etan-sulfonil)-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazina;

(3S)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-metil-pirrolidin-3-amina;

(3S)-N-etil-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-amina;

(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-(2,2,2-trifluoro-etil)-pirrolidin-3-amina;

acetato de 2-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-2-oxo-etilo;

acetato de {[(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-carbamoil}-metilo;

N-[(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-2-hidroxi-acetamida;

4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-1-metil-piperazin-2-ona;

4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-1-(2-hidroxi-etil)-piperazin-2-ona;

2-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-[4-(piperidin-1-il)-piperidin-1-il]-piridina;

{[1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-il]-metil}-dimetil-amina;

2-(4,4-dimetil-piperidin-1-il)-6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridina;

2-(3,3-dimetil-piperidin-1-il)-6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridina;

ácido 4-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-benzoico;

acetato de 1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-2-metil-1-oxo-propan-2-ilo;

acetato de (2S)-1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-1-oxo-propan-2-ilo;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N,N-dimetil-piperidin-4-amina;

N,N-dietil-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-sulfonamida;

N-etil-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-

imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-metil-piperidin-4-amina;

(2S)-1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-2-hidroxi-propan-1-ona;

1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-2-hidroxi-2-metil-propan-1-ona;

8-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-1,4-dioxa-8-aza-espiro-[4.5]-decano;

4-etil-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-ol;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-(propan-2-il)-piperidin-4-ol;

4-etenil-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-ol;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-metil-piperidin-4-ol;

2-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-{octahidro-pirrolo-[1,2-b]-piperazin-2-il}-piridina;

8-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-3-metil-1,3,8-triaza-espiro-[4.5]-decano-2,4-diona;

acetato de (1S)-1-{[(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-

il]-carbamoil}-etilo;

(2S)-N-[(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-2-hidroxi-propanamida;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-3-(trifluoro-metil)-piperazina;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-metil-piperidin-3-amina;

1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piridin-2-il]-N,N-dimetil-piperidin-4-amina;

acetato de 2-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-2-(trifluoro-metil)-piperazin-1-il]-2-oxo-etilo;

1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-2-(trifluoro-metil)-piperazin-1-il]-2-hidroxi-etan-1-ona;

1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piridin-2-il]-N-metil-piperidin-4-amina;

4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piridin-2-ol;

N-ciclobutil-6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-amina;

N-ciclopropil-6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-

imidazo-[1,2-b]-piridazin-3-il}-piridin-2-amina;

N-ciclopropil-1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piridin-2-il]-piperidin-4-amina;

1-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piridin-2-il]-piperidin-4-ona;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-(piridin-3-il)-piperazina;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-(piridin-2-il)-piperazina;

1-(4-fluoro-fenil)-4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazina;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-(6-metil-piridin-2-il)-piperazina;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-[5-(trifluoro-metil)-piridin-2-il]-piperazina;

2-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-N-metil-N-fenil-acetamida;

ácido 2-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-2-oxo-acético;

6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-carboxamida;

6-{6-[(2S)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-carboxamida;

2-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-etan-1-ol;

2-[4-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-N-(propan-2-il)-acetamida;

[1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-il]-metanol;

[1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-3-il]-metanol;

1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-carbonitrilo;

2-[4-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperazin-1-il]-etan-1-ol;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-ol;

2-fluoro-6-{6-[(2S)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridina;

2-fluoro-6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridina;

dietil-({2-[(6-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-amino]-etil})-amina;

1-(6-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-4-(propan-2-il)-piperazina;

(3S)-1-(6-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N,N-dimetil-pirrolidin-3-amina;

6-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-N-metil-piridin-2-amina;

6-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-N-(propan-2-il)-piridin-2-amina;

N-(6-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-metan-sulfonamida;

6-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-N,N-dimetil-piridin-2-amina;

2-{6-[2-(3-fluoro-fenil)-piperidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-(piperidin-4-iloxi)-piridina;

1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-ol;

(3R)-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N,N-dimetil-pirrolidin-3-amina;

1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-N-(2-hidroxi-etil)-piperidin-4-carboxamida;

N-[2-(dimetil-amino)-etil]-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-carboxamida;

ácido 1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-carboxílico;

N-(ciano-metil)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-

imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-carboxamida;

2-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirazina;

N-[(3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirrolidin-3-il]-acetamida;

1-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-1H-pirazol;

1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirazin-2-il)-piperidin-4-ol;

(3S)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirazin-2-il)-N,N-dimetil-pirrolidin-3-amina;

2-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-6-(piperazin-1-il)-pirazina;

2-[4-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirazin-2-il)-piperazin-1-il]-etan-1-ol;

(3R)-1-(6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-pirazin-2-il)-N,N-dimetil-pirrolidin-3-amina;

N-[1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-il]-acetamida;

1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-amina;

N-[1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-il]-metan-sulfonamida;

N-etil-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-amina;

N,N-dietil-1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-amina;

3-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-1H-pirrol;

N-[1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-il]-2-hidroxi-acetamida;

N-etil-N-[1-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-azetidin-3-il]-metan-sulfonamida;

1-[6-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piridin-2-il]-piperidin-4-ol;

6-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-2-oxa-6-aza-espiro-[3.3]-heptano;

6-[4-(6-{6-[(2R)-2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-pirimidin-2-il]-2-oxa-6-aza-espiro-[3.3]-heptano;

6-{6-[2-(3-fluoro-fenil)-pirrolidin-1-il]-imidazo-[1,2-b]-piridazin-3-il}-2,3-dihidro-1H-indol-2-ona;

6-{6-[3-(3-fluoro-fenil)-morfolin-4-il]-imidazo-[1,2-b]-piridazin-3-il}-2,3-dihidro-1H-indol-2-ona;

3-(3-fluoro-fenil)-4-{3-[6-(piperazin-1-il)-piridin-2-il]-imidazo-[1,2-b]-piridazin-6-il}-morfolina;

(3S)-4-[3-(6-fluoro-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il]-3-fenil-morfolina;

1-(6-{6-[(3S)-3-fenil-morfolin-4-il]-imidazo-[1,2-b]-

piridazin-3-il}-piridin-2-il)-piperidin-4-ol;

1-(6-{6-[3-(3-fluoro-fenil)-morfolin-4-il]-imidazo-[1,2-b]-piridazin-3-il}-piridin-2-il)-piperidin-4-carbaldehído;

3-(3-fluoro-fenil)-4-(3-{6-[4-(4-metil-1H-imidazol-2-il)-piperidin-1-il]-piridin-2-il}-imidazo-[1,2-b]-piridazin-6-il)-morfolina;

6-{6-[3-(3-fluoro-fenil)-morfolin-4-il]-imidazo-[1,2-b]-piridazin-3-il}-N,N-dimetil-piridin-2-amina;

3-(3-fluoro-fenil)-4-[3-(6-{4-[2-(metil-sulfanil)-etil]-piperazin-1-il}-piridin-2-il)-imidazo-[1,2-b]-piridazin-6-il]-morfolina;

3-(3-fluoro-fenil)-4-(3-{6-[4-(2-metan-sulfonil-etil)-piperazin-1-il]-piridin-2-il}-imidazo-[1,2-b]-piridazin-6-il)-morfolina;

(N-ciclopropil-1-(6-(6-(2-(3-fluoro-fenil)-pirrolidin-1-il)-imidazo-[1,2-b]-piridazin-3-il)-2,4'-bipiridin-2'-il)-piperidin-4-amina);

3-(3-fluoro-fenil)-4-(3-{6-[4-(1H-1,2,4-triazol-5-il)-piperidin-1-il]-piridin-2-il}-imidazo-[1,2-b]-piridazin-6-il)-morfolina, y

3-(3-fluoro-fenil)-4-(3-{6-[4-(1,2,4-oxadiazol-5-il)-piperidin-1-il]-piridin-2- il}-imidazo-[1,2-b]-piridazin-6-il)-morfolina.

21. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1 a 20, y un vehículo farmacéuticamente aceptable.

22. La composición farmacéutica de la reivindicación 21, en donde la composición farmacéutica se formula para administración intravenosa, administración oral, administración rectal, inhalación, administración nasal, administración tópica, administración oftálmica,

o administración ótica.

23. La composición farmacéutica de la reivindicación 21 o de la reivindicación 22, en donde la composición farmacéutica es una tableta, una píldora, una cápsula, un líquido, un inhalante, una solución de aspersión nasal, un supositorio, una solución, una emulsión, un ungüento, gotas para los ojos, o gotas para los oídos.

24. Un medicamento para el tratamiento de una enfermedad o condición mediada por cinasa en un paciente, en donde el medicamento comprende una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1 a 20, en donde la cinasa se selecciona a partir de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y ALK.

25. El uso de un compuesto de cualquiera de las reivindicaciones 1 a 20, en la elaboración de un medicamento para el tratamiento de una enfermedad o condición mediada por cinasa, en donde la cinasa se selecciona a partir de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y ALK.

26. Un método para inhibir una cinasa, el cual comprende administrar a un sistema o a un sujeto que lo necesite, una cantidad terapéuticamente efectiva de un compuesto de la fórmula (I), o sales farmacéuticamente aceptables o composiciones farmacéuticas del mismo, inhibiendo de esta manera la cinasa.

27. El método de la reivindicación 26, en donde la cinasa se

selecciona a partir de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y ALK, o una combinación de las mismas.

28. El método de la reivindicación 26, en donde la cinasa es TrkA, TrkB, TrkC o ALK.

29. Un método para el tratamiento de una enfermedad o condición mediada por cinasa, el cual comprende administrar a un sistema o a un sujeto que necesite dicho tratamiento, una cantidad efectiva de un compuesto de la fórmula (I), o sales farmacéuticamente aceptables o composiciones farmacéuticas del mismo, tratando de esta manera la condición, y en donde la cinasa se selecciona a partir de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y ALK, o una combinación de las mismas.

30. El método de la reivindicación 29, en donde la enfermedad o condición es cáncer, una enfermedad proliferativa, un trastorno de dolor, una enfermedad dermatológica, una enfermedad metabólica, una enfermedad muscular, una enfermedad neurodegenerativa, una enfermedad neurológica, una enfermedad de inmunodeficiencia, una enfermedad inmunológicamente mediada, una enfermedad autoinmune, una enfermedad auto-inmunológicamente mediada, una enfermedad ósea, una enfermedad inflamatoria, fibrosis, una enfermedad oftálmica, una enfermedad infecciosa, una enfermedad viral, reparación de heridas, una enfermedad respiratoria, una enfermedad pulmonar, una enfermedad renal, una

enfermedad del riñón, una enfermedad hepática, una enfermedad cardiovascular, una enfermedad vascular, una enfermedad cardíaca, muerte celular, y una enfermedad inflamatoria por hiperplasia.

31. El método de la reivindicación 30, en donde la enfermedad o condición es asma, enfermedad pulmonar obstructiva crónica (COPD), síndrome de insuficiencia respiratoria de adultos (ARDS), colitis ulcerativa, enfermedad de Crohn, bronquitis, dermatitis, rinitis alérgica, soriasis, esclerodermia, urticaria, artritis reumatoide, esclerosis múltiple, linfoma, metástasis, linfoma macrocelular anaplásico, osteosarcoma, fibrosarcoma, melanoma, cáncer de mama, cáncer renal, cáncer de cerebro, cáncer de próstata, cáncer colo-rectal, cáncer de tiroides, cáncer de ovario, cáncer pancreático, cáncer neuronal, neuroblastoma, cáncer de pulmón, cáncer uterino, cáncer gastrointestinal, VIH, o lupus.

32. Un método para el tratamiento de una condición proliferativa celular, el cual comprende administrar a un sistema o a un sujeto que necesite dicho tratamiento, una cantidad efectiva de un compuesto de la fórmula (I), o sales farmacéuticamente aceptables o composiciones farmacéuticas del mismo; en donde la condición proliferativa celular es linfoma, metástasis, linfoma macrocelular anaplásico, osteosarcoma, fibrosarcoma, melanoma, cáncer de mama, cáncer renal, cáncer de cerebro, cáncer de próstata, cáncer colo-rectal, cáncer de tiroides, cáncer de ovario, cáncer pancreático, cáncer neuronal, neuroblastoma, cáncer de pulmón, cáncer uterino o cáncer gastrointestinal.

33. El método de la reivindicación 32, en donde la condición proliferativa celular es linfoma macrocelular anaplásico, cáncer pancreático, cáncer de ovario y cáncer de pulmón.

34. Un compuesto para utilizarse en un método de tratamiento médico, en donde el método de tratamiento médico es para el tratamiento de una enfermedad seleccionada a partir de cáncer, una enfermedad proliferativa, un trastorno de dolor, una enfermedad dermatológica, una enfermedad metabólica, una enfermedad muscular, una enfermedad neurodegenerativa, una enfermedad neurológica, una enfermedad de inmunodeficiencia, una enfermedad inmunológicamente mediada, una enfermedad autoinmune, una enfermedad auto-inmunológicamente mediada, una enfermedad ósea, una enfermedad inflamatoria, fibrosis, una enfermedad oftálmica, una enfermedad infecciosa, una enfermedad viral, reparación de heridas, una enfermedad respiratoria, una enfermedad pulmonar, una enfermedad renal, una enfermedad del riñón, una enfermedad hepática, una enfermedad cardiovascular, una enfermedad vascular, una enfermedad cardíaca, una enfermedad inflamatoria por muerte celular e hiperplasia, y en donde el compuesto es un compuesto de cualquiera de las reivindicaciones 1 a 20.

35. El compuesto de la reivindicación 34, en donde la enfermedad es asma, enfermedad pulmonar obstructiva crónica (COPD), síndrome de insuficiencia respiratoria de adultos (ARDS), colitis ulcerativa, enfermedad de Crohn, bronquitis, dermatitis, rinitis

alérgica, soriasis, esclerodermia, urticaria, artritis reumatoide, esclerosis múltiple, linfoma, metástasis, linfoma macrocelular anaplásico, osteosarcoma, fibrosarcoma, melanoma, cáncer de mama, cáncer renal, cáncer de cerebro, cáncer de próstata, cáncer colo-rectal, cáncer de tiroides, cáncer de ovario, cáncer pancreático, cáncer neuronal, neuroblastoma, cáncer de pulmón, cáncer uterino, cáncer gastrointestinal, VIH, o lupus.

RESUMEN

La invención proporciona compuestos, composiciones farmacéuticas que comprenden estos compuestos, y métodos para utilizar tales compuestos con el fin de tratar o prevenir las enfermedades o los trastornos asociados con una actividad de cinasa anormal o mal regulada, en particular de Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 y ALK, o combinaciones de las mismas.

* * * * *

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:

GENOMICS INSTITUTE OF THE NOVARTIS RESEARCH FOUNDATION
Attn. Raymond, Daniel E.
10675 John Jay Hopkins Drive
San Diego, CA 92121
ETATS-UNIS D'AMERIQUE

GNF Legal Department
RECEIVED
NOV - 5 2009
BY:

Applicant's or agent's file reference P1316PC20	Date of mailing *(day/month/year)* 03/11/2009 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2009/043073	International filing date *(day/month/year)* 07/05/2009
Applicant IRM LLC	

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Isabelle Lombart

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1–10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion 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 (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
P1316PC20		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2009/043073	07/05/2009	13/05/2008
Applicant		
IRM LLC		

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

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] 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))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:

   FUSED NITROGEN CONTAINING HETEROCYCLES AND COMPOSITIONS THEREOF AS KINASE INHIBITORS

5. With regard to the **abstract,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

A50

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/043073

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with abnormal or deregulated kinase activity, particularly Ros, KDR, FMS, c-FMS, FLT3, c-Kit, JAK2, JAK3, Aurora, PDGFR, Lck, TrkA, TrkB, TrkC, IGF-1R, ALK4, ALK5 and ALK or combinations thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/043073

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D487/04 A61K31/4353 A61K31/4985 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/00213 A (MERCK & CO INC [US]; ARMSTRONG HELEN M [US]; BERESIS RICHARD [US]; GOU) 4 January 2001 (2001-01-04) abstract examples 234-240,266-268,385-391 claims 1,13-39	1-35
Y	US 2007/093490 A1 (PRIEN OLAF [DE] ET AL) 26 April 2007 (2007-04-26) abstract examples claims 1,17-20	1-35

☐ Further documents are listed in the continuation of Box C.

☒ 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
27 October 2009	03/11/2009

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	Stix-Malaun, Elke

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/043073

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0100213 A	04-01-2001	AT 253915 T	15-11-2003
		AU 5636900 A	31-01-2001
		CA 2383546 A1	04-01-2001
		DE 60006541 D1	18-12-2003
		EP 1206265 A1	22-05-2002
		JP 2003523942 T	12-08-2003
US 2007093490 A1	26-04-2007	NONE	

PATENT COOPERATION TREATY

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/US2009/043073	07.05.2009	13.05.2008

International Patent Classification (IPC) or both national classification and IPC
INV. C07D471/04 C07D487/04 A61K31/4353 A61K31/4985 A61P37/00

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	Stix-Malaun, Elke Telephone No. +49 89 2399-8057

Form PCT/ISA/237 (Cover Sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2009/043073

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. 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	1-35
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-35
Industrial applicability (IA)	Yes:	Claims	1-35
	No:	Claims	

2. Citations and explanations

see separate sheet

V REASONED STATEMENT

1. PRIOR ART

The documents cited in the International Search Report

D1: WO 01/00213 A (MERCK & CO INC [US]; ARMSTRONG HELEN M [US]; BERESIS RICHARD [US]; GOU) 4 January 2001 (2001-01-04)
D2: US 2007/093490 A1 (PRIEN OLAF [DE] ET AL) 26 April 2007 (2007-04-26)

have been considered for the examination procedure.

2. GENERAL STATEMENT

Claim 26-33 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1 (iv)/Rule 67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognize 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 in a first or further medical treatment.

3. NOVELTY

The subject-matter of the claims is considered to be a novel selection from D1 and D2 on account of the position and nature of R1(Article 33(2) PCT).

4. INVENTIVE STEP

The subject-matter of the claims does not fulfil the requirements of Article 33(3) PCT for the following reasons:

The application relates to fused nitrogen containing heterocycles useful as proteine kinase inhibitors for the treatment of proliferative diseases,neurological diseases and immunodeficiency diseases.

The closest state of the art for the present application is represented by D1 and D2. Said documents disclose structurally similar fused nitrogen containing cycles that form an overlapping part with the present generic expression.

D1 teaches a broad scope of possible variations. D2 discloses a specific substitution pattern. Moreover D1 discloses examples exhibiting the same substitution pattern as claimed differing only very little in the respective definition of present R1,namely the fusion of the saturated nitrogen containing heterocycle.

Such a selection can only be regarded as inventive, if the present application exhibits unexpected effects or properties in relation to the rest of the range of D1 (see for examples 235 and 239). However, no such effects or properties are indicated in the application. In the absence of comparative test results or other appropriate information it is not possible to decide whether such a problem has been solved or not.

PATENT COOPERATION TREATY

PCT/US2009/043073

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)*
20 October 2010 (20.10.2010)

Applicant's or agent's file reference
P1316PC20

IMPORTANT NOTIFICATION

International application No.
PCT/US2009/043073

International filing date *(day/month/year)*
07 May 2009 (07.05.2009)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address
IRM LLC
131 Front Street
P.O Box 2899
Bermuda
Hamilton, HM LX
Bermuda

State of Nationality: US
State of Residence: US
Telephone No.: 858-812-1617
Facsimile No.: 858-812-1909
E-mail address: iplegal@gnf.org

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
IRM LLC
131 Front Street
P.O Box HM 2899
Hamilton HM LX
Bermuda

State of Nationality: US
State of Residence: US
Telephone No.: 858-812-1617
Facsimile No.: 858-812-1909
E-mail address: iplegal@gnf.org
☐ 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

Facsimile No. +41 22 338 71 30

Authorized officer
Agrati Fanny
e-mail pt09.pct@wipo.int
Telephone No. +41 22 338 74 09

Form PCT/IB/306 (January 2009)

1/EMV6K5140

455

PATENT COOPERATION TREATY PCT/US2009/043073

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)*
20 October 2010 (20.10.2010)

Applicant's or agent's file reference
P1316PC20

IMPORTANT NOTIFICATION

International application No.
PCT/US2009/043073

International filing date *(day/month/year)*
07 May 2009 (07.05.2009)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

CHOPIUK, Gregory
10994 West Ocean Air Drive, Apt. 387
San Diego, CA 92130
United States of America

State of Nationality	State of Residence
CA	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

CHOPIUK, Gregory
2055 Pendrell Street, Suite 803
Vancouver, British Columbia V6G 1T9
Canada

State of Nationality	State of Residence
CA	CA

Telephone No.

Facsimile No.

E-mail address
☐ Notifications by e-mail authorized

3. Further observations, if necessary:
The new agent's file reference is: PAT052874- WO-PCT .

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

Facsimile No. +41 22 338 71 30

Authorized officer
Agrati Fanny
e-mail pt09.pct@wipo.int
Telephone No. +41 22 338 74 09

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-153711- -00000-0000
Fecha: 2010-12-06 17:39:02 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 455

PATENTE DE INVENCIÓN ☐ MODELO DE UTIL

- ☐ 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 ☐

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
IRM LLC

REFERENCIA		
	Radicación No.	10 153711
	Solicitud internacional	PCT/US2009/043073
	Fecha inicio fase nacional	13/12/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	00425

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...

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista de fecha 07 ENE. 2011.
adpa11

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
IRM LLC

REFERENCIA	Radicación No.	10 153711
	Solicitud internacional	PCT/US2009/043073
	Fecha inicio fase nacional	13/12/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	0 0 4 2 6

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.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista de fecha 07 ENE. 2011
adpa11