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Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISION DE NUEVAS CREACIONES

09-70739

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

SOLICITUD DE PATENTE DE INVENCION

TITULO COMPUESTOS Y COMPOSICIONES COMO INHIBIDORES DE LA PROTEINA QUINASA

SOLICITANTE IRM LLC

DIRECCION 131 Front Street, P O Box HM 2899, Hamilton HM LX, Bermuda

APODERADO CARLOS R OLARTE

BOGOTA 08 de Julio de 2009

P2009/000099

OLARTERAISBECK
OLARTE RAISBECK MOURE

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-070739- -00000-0000
Fecha: 2009-07-08 17:00:29 Dep: 2020 NUECREACIONE
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 418

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2009/000099**

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

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Número 79782747Bta
TP 74.295

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Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2007/085304 Fecha Noviembre 20, 2007

Publicación Internacional No. WO 2008/073687 Fecha Junio 19, 2008

(6) **Título (54)** **COMPUESTOS Y COMPOSICIONES COMO INHIBIDORES DE LA PROTEINA QUINASA**

Clasificación Internacional (51) C07D 213/74, C07D 239/48, C07D 239/95, C07D 401/12

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Diciembre 8, 2006	60/869.299
US	Agosto 28, 2007	60/966.449

(9) **Comprobante de pago No.** 09-47,662 **Fecha** 01 de julio de 2009

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. 06.122.179
- [ ] 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.
- [ ] 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.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-070739- -00000-0000
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Act. 411 PRESENTACION Folios: 418

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 47,662
FECHA : JULIO 1 DE 2009

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARIE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	110378903	01/07/2009	7,760,000.00

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	540,000.00
		TOTAL : $	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

El documento de Poder adjunto de IRM LLC. a Delaware Limited Liability Company lleva la siguiente certificación notarial:

CERTIFICACIÓN

Yo, el suscrito Notario Público de Basilea, Suiza, certifico la autenticidad de las firmas anteriores correspondientes al Dr. Dirk Hillebrand, ciudadano Alemán, residente en Bad Säckingen, Alemania y al Dr. Peter Roth, ciudadano Aleman, residente en Friburgo, Alemania, ambos actuando en nombre de IRM LLC, en Hamilton, Bermuda, ambos apoderados, ambos con firma mancomunada.

La autenticidad de las firmas se estableció por comparación.

Basilea, este día 20 (veinte) de Noviembre de 2006 (dos mil seis).

(Firmado)

Sello: "Dr. Mattias Staehelin – Notario de Basilea"

Protocolo de Legalización No. 1571/2006

Apostilla:

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

6

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

1. País:	Suiza
El presente documento público	
2. Ha sido firmado por:	Dr. M. Staehelin
3. Actuando en calidad de:	Notario
4. Lleva el sello/estampilla de:	(Ilegible).
Certificado	
5. En:	Basilea.
6. El:	20 de Noviembre de 2006.
7. Por:	Cancillería municipal del Cantón de la ciudad de Basilea.
8. Bajo el No.:	10413/17.594
9. Sello / estampilla:	Cancillería municipal · Ciudad de Basilea.
10. Firma:	Heidi Fischer

Certificación:

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

Título: "IRM LLC – Cert."

Fecha: 29 de Noviembre de 2006.

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Simón Salinas

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Graciela Melo

33842-CO-PCT

Power of Attorney

Poder

The undersigned,

El suscrito,

IRM LLC, a Delaware Limited Liability Company

domiciled in

domiciliado en

'Hurst Holme', 12 Trott Road, Hamilton, Bermuda, HM 11

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

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

IRM LLC, a Delaware Limited Liability Company

Signature/Firma:

Dirk Hillebrand
Group Head Patents, MCD

Peter Roth
Snr. Patent Attorney

Date/Fecha: 08 November 2006

City,Country/Ciudad,País: Basel, CH

Attestation

I, the undersigned notary public in Basel, Switzerland, certify herewith that the above signatures are the genuine signatures of **Dr. Dirk Hillebrand**, German citizen, residing in Bad Säckingen, Germany, and **Dr. Peter Roth**, German citizen, residing in Freiburg, Germany, 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, this 20th (twentieth) day of November 2006 (twothousandandsix).

DR. MATTHIAS STAEHELIN NOTAR BASEL

M. Staehelin, Notar

Leg.Prot.Nr. 1591 /2006

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Confederation)

This official document

2. is signed by .....

3. in his/her function of .....

4. and certified by .....

Certified 20. NOV. 2006

5. in Basel (BS) 6. on .....

7. by the State Chancery of the Canton of Basel-Stadt .....

8. under No .....

9. Seal/Stamp: STAATSKANZLEI * BASEL-STADT

10. Signature:

Heidi Fischer

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

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International Bureau

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, 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, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:
— *without international search report and to be republished upon receipt of that report*

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

(57) Abstract: The invention provides novel pyrimidine and pyridine derivatives and pharmaceutical compositions thereof, and methods for using such compounds. For example, the pyrimidine and pyridine derivatives of the invention may be used to treat, ameliorate or prevent a condition which responds to inhibition of anaplastic lymphoma kinase (ALK) activity, focal adhesion kinase (FAK), zeta-chain-associated protein kinase 70 (ZAP-70), insulin-like growth factor (IGF-1R), or a combination thereof.

WO 2008/073687 A2

COMPOUNDS AND COMPOSITIONS AS PROTEIN KINASE INHIBITORS

Cross-Reference to Related Applications

[0001] This application claims the benefit of U.S. provisional application serial no. 60/869,299, filed December 8, 2006, which is incorporated by reference herein in its entirety.

Technical Field

[0002] The invention relates to protein kinase inhibitors, more particularly novel pyrimidine and pyridine derivatives and pharmaceutical compositions thereof, and their use as pharmaceuticals.

Background Art

[0003] Anaplastic lymphoma kinase (ALK), a member of the insulin receptor superfamily of receptor tyrosine kinases, has been implicated in oncogenesis in hematopoietic and non-hematopoietic tumors. The aberrant expression of full-length ALK receptor proteins has been reported in neuroblastomas and glioblastomas; and ALK fusion proteins have occurred in anaplastic large cell lymphoma. The study of ALK fusion proteins has also raised the possibility of new therapeutic treatments for patients with ALK-positive malignancies. (Pulford et al., Cell. Mol. Life Sci. 61:2939-2953 (2004)).

[0004] Focal Adhesion Kinase (FAK) is a key enzyme in the integrin-mediated outside-in signal cascade (D. Schlaepfer et al., Prog Biophys Mol Biol 1999, 71, 43578). The trigger in the signal transduction cascade is the autophosphorylation of Y397. Phosphorylated Y397 is a SH2 docking site for Src family tyrosine kinases; the bound c-Src kinase phosphorylates other tyrosine residues in FAK. Among them, phsophorylated Y925 becomes a binding site for the SH2 site of Grb2 small adaptor protein. This direct binding of Grb2 to FAK is one of the key steps for the activation of down stream targets such as the Ras-ERK2/MAP kinase cascade.

[0005] Zeta-chain-associated protein kinase 70 (ZAP-70), a member of the protein tyrosine kinase family, is of potential prognostic importance in chronic lymphocytic leukemia (CLL). ZAP-70, known to be of importance in T and NK cell signaling but absent in normal peripheral B cells, is expressed in the majority of the poorer prognosis unmutated CLL and absent in most cases with mutated IgVH genes. ZAP-70 is also expressed in a minority of other B cell tumors. (Orchard et al., Leuk. Lymphoma 46:1689-98 (2005)).

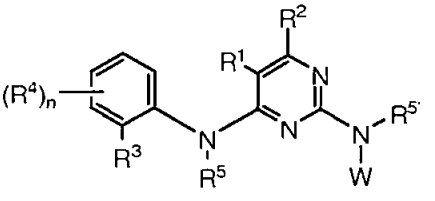
[0006] Insulin-like growth factor (IGF-1) signaling is highly implicated in cancer, with the IGF-1 receptor (IGF-1R) as the predominating factor. IGR-1R is important for tumor transformation and survival of malignant cells, but is only partially involved in normal cell growth. Targeting of IGF-1R has been suggested to be a promising option for cancer therapy. (Larsson et al., Br. J. Cancer 92:2097-2101 (2005)).

[0007] Because of the emerging disease-related roles of ALK, FAK, ZAP-70 and IGF-1R, there is a continuing need for compounds which may be useful for treating and preventing a disease which responds to inhibition of ALK, FAK, ZAP-70 and/or IGF-1R.

Disclosure of the Invention

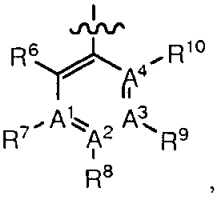
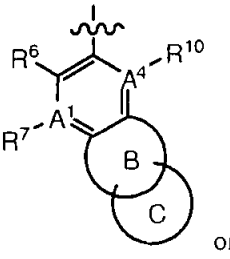
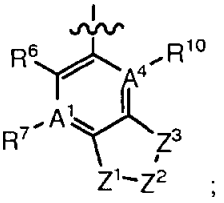
[0008] The invention relates to novel pyrimidine and pyridine derivatives and pharmaceutical compositions thereof, and their use as pharmaceuticals.

[0009] In one aspect, the invention provides a having Formula (1):



(1)

or pharmaceutically acceptable salts thereof; wherein

W is  ,  or  ;

A^1 and A^4 are independently C or N;

each A^2 and A^3 is C, or one of A^2 and A^3 is N when R^6 and R^7 form a ring;

B and C are independently an optionally substituted 5-7 membered carbocyclic ring, aryl, heteroaryl or heterocyclic ring containing N, O or S;

Z^1, Z^2 and Z^3 are independently NR^{11}, C=O, CR-OR, $(CR_2)_{1-2}$ or $=C-R^{12}$;

R^1 and R^2 are independently halo, OR^{12}, $NR(R^{12})$, SR^{12}, or an optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; or one of R^1 and R^2 is H;

R^3 is $(CR_2)_{0-2}SO_2R^{12}$, $(CR_2)_{0-2}SO_2NRR^{12}$, $(CR_2)_{0-2}CO_{1-2}R^{12}$, $(CR_2)_{0-2}CONRR^{12}$ or cyano;

R^4, R^6, R^7 and R^{10} are independently an optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; OR^{12}, $NR(R^{12})$, halo, nitro, SO_2R^{12}, $(CR_2)_pR^{13}$ or X; or R^4, R^7 and R^{10} are independently H;

R, R^5 and $R^{5'}$ are independently H or C_{1-6} alkyl;

R^8 and R^9 are independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo or X, or one of R^8 and R^9 is H when R^1 and R^2 form a ring; and provided one of R^8 and R^9 is X;

alternatively, R^1 and R^2, or R^6 and R^7, R^7 and R^8, or R^9 and R^{10}, when attached to a carbon atom may form an optionally substituted 5-7 membered monocyclic or fused carbocyclic ring, aryl, or heteroaryl or heterocyclic ring comprising N, O and/or S; or R^7, R^8, R^9 and R^{10} are absent when attached to N;

R^{11} is H, C_{1-6} alkyl, C_{2-6} alkenyl, $(CR_2)_pCO_{1-2}R$, $(CR_2)_pOR$, $(CR_2)_pR^{13}$, $(CR_2)_pNRR^{12}$, $(CR_2)_pCONRR^{12}$ or $(CR_2)_pSO_{1-2}R^{12}$;

R^{12} and R^{13} are independently an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, or a 5-7 membered heterocyclic ring comprising N, O and/or S; aryl or heteroaryl; or R^{12} is H, C_{1-6} alkyl;

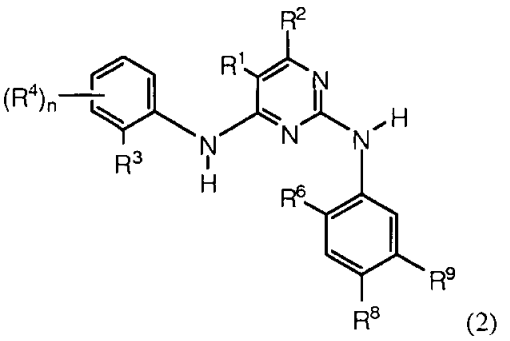
X is $(CR_2)_qY$, cyano, $CO_{1-2}R^{12}$, $CONR(R^{12})$, $CONR(CR_2)_pNR(R^{12})$, $CONR(CR_2)_pOR^{12}$, $CONR(CR_2)_pSR^{12}$, $CONR(CR_2)_pS(O)_{1-2}R^{12}$ or $(CR_2)_{1-6}NR(CR_2)_pOR^{12}$;

Y is an optionally substituted 3-12 membered carbocyclic ring, a 5-12 membered aryl, or a 5-12 membered heteroaryl or heterocyclic ring comprising N, O and/or S and attached to A^2 or A^3 or both via a carbon atom of said heteroaryl or heterocyclic ring when q in $(CR_2)_qY$ is 0; and

n, p and q are independently 0-4.

[0010] In the above Formula (1), R^1 may be halo or C_{1-6} alkyl; R^2 is H or NH_2; or R^1 and R^2 together form an optionally substituted 5-6 membered aryl, or heteroaryl or heterocyclic ring comprising 1-3 nitrogen atoms. In other examples, R^3 in Formula (1) may be SO_2R^{12}, SO_2NH_2, SO_2NRR^{12}, CO_2NH_2, $CONRR^{12}$, $CO_{1-2}R^{12}$, or cyano; and R^{12} is C_{1-6} alkyl, an optionally substituted C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl or azetidinyl. In yet other examples, R^5, $R^{5'}$, R^7 and R^{10} in Formula (1) are independently H, and n is 0. In other examples, R^6 in Formula (1) may be halo or OR^{12}, and R^{12} is C_{1-6} alkyl.

[0011] In one embodiment, the invention provides compounds having Formula (2):



(2)

wherein R^1 is halo or C_{1-6} alkyl;

R^2 is H; or

R^1 and R^2 together form an optionally substituted 5-6 membered heteroaryl or heterocyclic ring comprising one or two nitrogen atoms;

R^6 is isopropoxy or methoxy;

one of R^8 and R^9 is $(CR_2)_qY$ and the other is C_{1-6} alkyl, cyano, $CO_{1-2}R^{12}$, $CONR(R^{12})$ or $CONR(CR_2)_pNR(R^{12})$;

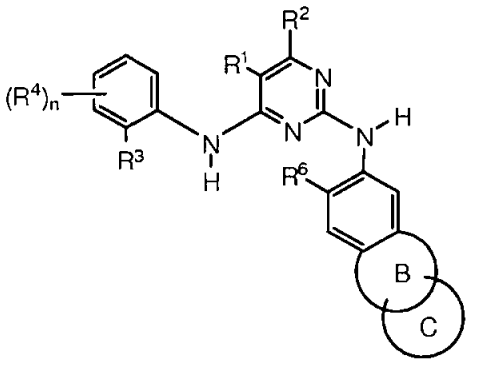
Y is an optionally substituted C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, or phenyl; or Y is pyridyl, pyrazolyl, isoxazolyl, imidazolyl, thiazolyl, benzimidazolyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, azetidinyl, heptamethyleneimine or octamethyleneimine, each of which is attached to the phenyl ring via a carbon atom when q in $(CR_2)_qY$ is 0;

n is 0-1; and

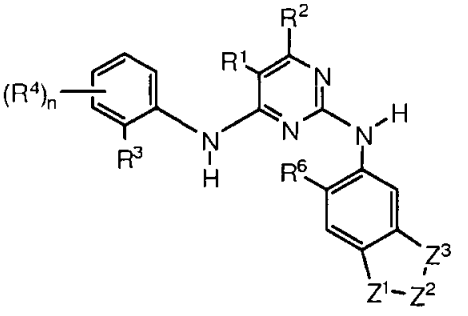
q is 0-4.

[0012] In the above Formula (2), one of R^8 and R^9 may be $(CR_2)_qY$ and the other is C_{1-6} alkyl; and n and q are independently 0. In some examples, Y is pyrrolidinyl, piperidinyl, azetidinyl. In other examples, R^1 is halo or C_{1-6} alkyl; and R^2 is H.

[0013] In another embodiment, the invention provides compounds having Formula (3A) or (3B):

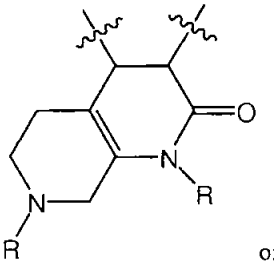


(3A)

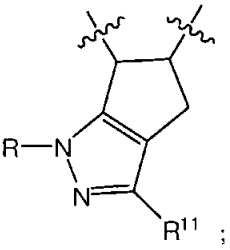


(3B)

wherein B and C together form

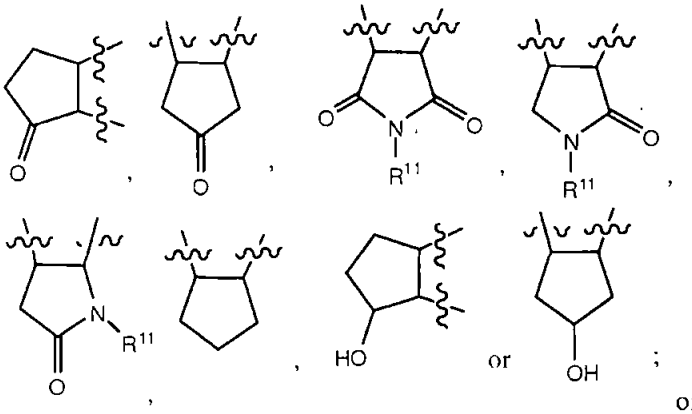


or



;

Z^1, Z^2 and Z^3 together form



or tautomers thereof;

R^1 is halo or C_{1-6} alkyl;

R^2 is H; or

R^1 and R^2 together form an optionally substituted 5-7 membered carbocyclic ring, aryl, or heteroaryl or heterocyclic ring comprising N, O and/or S; and

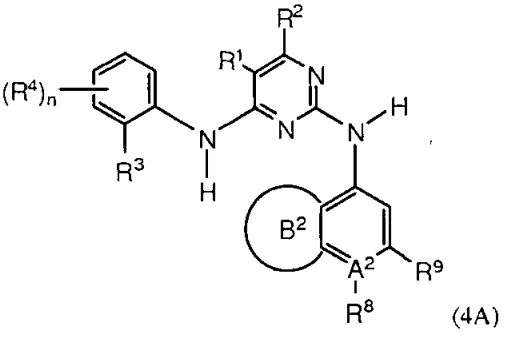
R^6 is isopropoxy or methoxy.

[0014] In the above Formula (3A) or (3B), each R^{11} may be $(CR_2)_pCO_{1-2}R$, $(CR_2)_pOR$, $(CR_2)_pR^{13}$, $(CR_2)_pNRR^{12}$ or $(CR_2)_pCONRR^{12}$;

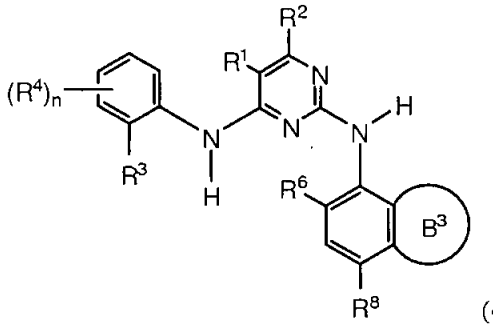
R and R^{12} are independently H or C_{1-6} alkyl; and

R^{13} is an optionally substituted piperidinyl, azetidiyl, tetrahydropyranyl, cyclohexyl, morpholinyl, pyrrolidinyl, heptamethyleneimine, octamethyleneimine, a bicyclic amine or diamine derivative, quinuclidin-3-yl, 8-methyl-8-aza-bicyclo[3.2.1]oct-6-yl], or 9-methyl-9-aza-bicyclo[4.2.1]nonan-7-yl.

[0015] In yet another embodiment, the invention provides compounds having Formula (4A) or Formula (4B):



(4A)



(4B);

wherein R^1 is halo or C_{1-6} alkyl;

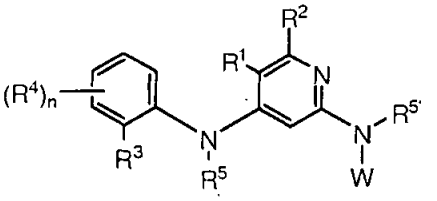
R^2 is H; or

R^1 and R^2 together form an optionally substituted 5-7 membered carbocyclic ring, aryl, or heteroaryl or heterocyclic ring comprising N, O and/or S;

R^6 is isopropoxy or methoxy; and

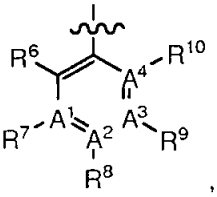
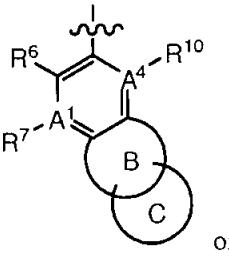
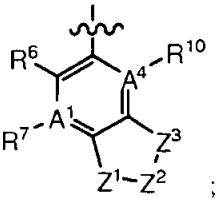
B^2 and B^3 are independently an optionally substituted 5-6 membered aryl or heteroaryl containing N, O or S.

[0016] In another aspect, the invention provides compounds having Formula (5):



(5)

or pharmaceutically acceptable salts thereof; wherein

W is  ,  or  ;

A^1 and A^4 are independently C or N;

each A^2 and A^3 is C, or one of A^2 and A^3 is N when R^6 and R^7 form a ring;

B and C are independently an optionally substituted 5-7 membered carbocyclic ring, aryl, heteroaryl or heterocyclic ring containing N, O or S;

Z^1, Z^2 and Z^3 are independently NR^{11}, C=O, CR-OR, $(CR_2)_{1-2}$ or $=C-R^{12}$;

R^1 and R^2 are independently halo, OR^{12}, $NR(R^{12})$, SR^{12}, or an optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; or one of R^1 and R^2 is H;

R^3 is $(CR_2)_{0-2}SO_2R^{12}$, $(CR_2)_{0-2}SO_2NRR^{12}$, $(CR_2)_{0-2}CO_{1-2}R^{12}$, $(CR_2)_{0-2}CONRR^{12}$ or cyano;

R^4, R^6, and R^7 and R^{10} when attached to a carbon atom, are independently H, an optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; OR^{12}, $NR(R^{12})$, halo, nitro, SO_2R^{12}, $(CR_2)_pR^{13}$ or X; provided R^6 and R^7 are not both H;

R, R^5 and $R^{5'}$ are independently H or C_{1-6} alkyl;

R^8 and R^9 are independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo or X, or one of R^8 and R^9 is H; and provided one of R^8 and R^9 is X;

alternatively, R^1 and R^2, or R^6 and R^7, R^7 and R^8, or R^9 and R^{10}, when attached to a carbon atom may form an optionally substituted 5-7 membered monocyclic or fused carbocyclic ring, aryl, or heteroaryl or heterocyclic ring comprising N, O and/or S; or R^7, R^8, R^9 and R^{10} are absent when attached to N;

R^{11} is H, C_{1-6} alkyl, C_{2-6} alkenyl, $(CR_2)_pCO_{1-2}R$, $(CR_2)_pOR$, $(CR_2)_pR^{13}$, $(CR_2)_pNRR^{12}$, $(CR_2)_pCONRR^{12}$ or $(CR_2)_pSO_{1-2}R^{12}$;

R^{12} and R^{13} are independently an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, or a 5-7 membered heterocyclic ring comprising N, O and/or S; aryl or heteroaryl; or R^{12} is H, C_{1-6} alkyl;

X is $(CR_2)_qY$, cyano, $CO_{1-2}R^{12}$, $CONR(R^{12})$, $CONR(CR_2)_pNR(R^{12})$, $CONR(CR_2)_pOR^{12}$, $CONR(CR_2)_pSR^{12}$, $CONR(CR_2)_pS(O)_{1-2}R^{12}$ or $(CR_2)_{1-6}NR(CR_2)_pOR^{12}$;

Y is an optionally substituted 3-12 membered carbocyclic ring, a 5-12 membered aryl, or a 5-12 membered heteroaryl or heterocyclic ring comprising N, O and/or S and attached to A^2 or A^3 or both via a carbon atom of said heteroaryl or heterocyclic ring when q in $(CR_2)_qY$ is 0; and

n, p and q are independently 0-4.

[0017] In yet another aspect, the present invention provides pharmaceutical compositions comprising a compound having Formula (1), (2), (3A), (3B), (4A), (4B) or (5), and a pharmaceutically acceptable excipient.

[0018] In yet another aspect, the invention provides methods for modulating ALK, FAK, ZAP-70 and/or IGF-1R, comprising administering to a system or a subject in need thereof, a therapeutically effective amount of a compound having Formula (1), (2), (3A), (3B), (4A), (4B) or (5), or pharmaceutically acceptable salts or pharmaceutical compositions thereof, thereby modulating said ALK, FAK, ZAP-70 and/or IGF-1R. The invention also provides methods to

treat, ameliorate or prevent a condition which responds to inhibition of ALK, FAK, ZAP-70 and/or IGF-1R, comprising administering to a system or subject in need of such treatment an effective amount of a compound having Formula (1), (2), (3A), (3B), (4A), (4B) or (5), or pharmaceutically acceptable salts or pharmaceutical compositions thereof, and optionally in combination with a second therapeutic agent, thereby treating said condition. Alternatively, the present invention provides the use of a compound having Formula (1), (2), (3A), (3B), (4A), (4B) or (5) in the manufacture of a medicament for treating a condition mediated by ALK, FAK, ZAP-70 and/or IGF-1R. In particular embodiments, the compounds of the invention may be used alone or in combination with a second therapeutic agent to treat a condition mediated by ALK, wherein said condition is an autoimmune disease, a transplantation disease, an infectious disease or a cell proliferative disorder.

[0019] Furthermore, the invention provides methods for treating a cell proliferative disorder, comprising administering to a system or subject in need of such treatment an effective amount of a compound having Formula (1), (2), (3A), (3B), (4A), (4B) or (5), or pharmaceutically acceptable salts or pharmaceutical compositions thereof, and optionally in combination with a second therapeutic agent, thereby treating said condition. Alternatively, the present invention provides the use of a compound having Formula (1), (2), (3A), (3B), (4A), (4B) or (5) in the manufacture of a medicament for treating a cell-proliferative disorder. In particular examples, the compounds of the invention may be used alone or in combination with a chemotherapeutic agent to treat a cell proliferative disorder, including but not limited to, lymphoma, osteosarcoma, melanoma, or a tumor of breast, renal, prostate, colorectal, thyroid, ovarian, pancreatic, neuronal, lung, uterine or gastrointestinal tumor.

[0020] In the above methods for using the compounds of the invention, a compound having Formula (1), (2), (3A), (3B), (4A), (4B) or (5) may be administered to a system comprising cells or tissues, or to a mammalian subject such as a human or animal subject.

Definitions

[0021] "Alkyl" refers to a moiety and as a structural element of other groups, for example halo-substituted-alkyl and alkoxy, and may be straight-chained or branched. An optionally substituted alkyl, alkenyl or alkynyl as used herein may be optionally halogenated (e.g., CF_3), or may have one or more carbons that is substituted or replaced with a heteroatom, such as NR, O or S (e.g., $-OCH_2CH_2O-$, alkylthiols, thioalkoxy, alkylamines, etc).

[0022] "Aryl" refers to a monocyclic or fused bicyclic aromatic ring containing carbon atoms. "Arylene" means a divalent radical derived from an aryl group. For example, an aryl group may be phenyl, indenyl, indanyl, naphthyl, or 1,2,3,4-tetrahydronaphthalenyl, which may be optionally substituted in the ortho, meta or para position.

[0023] "Heteroaryl" as used herein is as defined for aryl above, where one or more of the ring members is a heteroatom. Examples of heteroaryls include but are not limited to pyridyl, pyrazinyl, indolyl, indazolyl, quinoxalinyl, quinolinyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzo[1,3]dioxole, imidazolyl, benzo-imidazolyl, pyrimidinyl, furanyl, oxazolyl, isoxazolyl, triazolyl, benzotriazolyl, tetrazolyl, pyrazolyl, thienyl, pyrrolyl, isoquinolinyl, purinyl, thiazolyl, tetrazinyl, benzothiazolyl, oxadiazolyl, benzoxadiazolyl, etc.

[0024] A "carbocyclic ring" as used herein refers to a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring containing carbon atoms, which may optionally be substituted, for example, with =O. Examples of carbocyclic rings include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylene, cyclohexanone, etc.

[0025] A "heterocyclic ring" as used herein is as defined for a carbocyclic ring above, wherein one or more ring carbons is a heteroatom. For example, a heterocyclic ring may contain N, O, S, -N=, -S-, -S(O), -$S(O)_2$-, or -NR- wherein R may be hydrogen, C_{1-4}alkyl or a protecting group. Examples of heterocyclic rings include but are not limited to morpholino, pyrrolidinyl, pyrrolidinyl-2-one, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, 1,2,3,4-tetrahydroquinolinyl, etc. Heterocyclic rings as used herein may encompass bicyclic amines and bicyclic diamines.

[0026] 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.

[0027] The term "pharmaceutical combination" as used herein refers to a product obtained from mixing or combining active ingredients, 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 (1) and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of Formula (1) 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 active ingredients in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

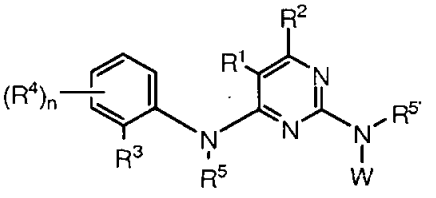
[0028] The term "therapeutically effective amount" means the amount of the subject compound that will elicit a biological or medical response in a cell, tissue, organ, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

[0029] 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.

Modes of Carrying Out the Invention

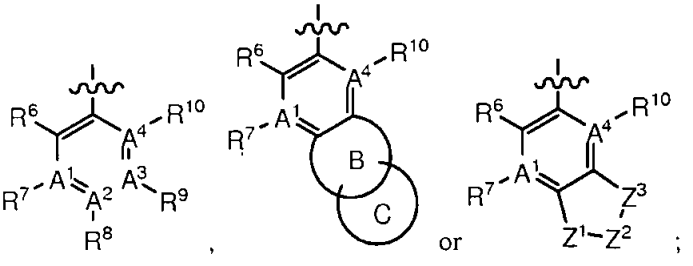
[0030] The invention provides novel pyrimidine and pyridine derivatives and pharmaceutical compositions thereof, and methods for using such compounds.

[0031] In one aspect, the invention provides a having Formula (1):



(1)

or pharmaceutically acceptable salts thereof; wherein



W is , or ;

A^1 and A^4 are independently C or N;

each A^2 and A^3 is C, or one of A^2 and A^3 is N when R^6 and R^7 form a ring;

B and C are independently an optionally substituted 5-7 membered carbocyclic ring, aryl, heteroaryl or heterocyclic ring containing N, O or S;

Z^1, Z^2 and Z^3 are independently NR^{11}, C=O, CR-OR, $(CR_2)_{1-2}$ or =C-R^{12};

R^1 and R^2 are independently halo, OR^{12}, $NR(R^{12})$, SR^{12}, or an optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; or one of R^1 and R^2 is H;

R^3 is $(CR_2)_{0-2}SO_2R^{12}$, $(CR_2)_{0-2}SO_2NRR^{12}$, $(CR_2)_{0-2}CO_{1-2}R^{12}$, $(CR_2)_{0-2}CONRR^{12}$ or cyano;

R^4, R^6, R^7 and R^{10} are independently an optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; OR^{12}, $NR(R^{12})$, halo, nitro, SO_2R^{12}, $(CR_2)_pR^{13}$ or X; or R^4, R^7 and R^{10} are independently H;

R, R^5 and $R^{5'}$ are independently H or C_{1-6} alkyl;

R^8 and R^9 are independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo or X, or one of R^8 and R^9 is H when R^1 and R^2 form a ring; and provided one of R^8 and R^9 is X;

alternatively, R^1 and R^2, or R^6 and R^7, R^7 and R^8, or R^9 and R^{10}, when attached to a carbon atom may form an optionally substituted 5-7 membered monocyclic or fused carbocyclic ring, aryl, or heteroaryl or heterocyclic ring comprising N, O and/or S; or R^7, R^8, R^9 and R^{10} are absent when attached to N;

R^{11} is H, C_{1-6} alkyl, C_{2-6} alkenyl, $(CR_2)_pCO_{1-2}R$, $(CR_2)_pOR$, $(CR_2)_pR^{13}$, $(CR_2)_pNRR^{12}$, $(CR_2)_pCONRR^{12}$ or $(CR_2)_pSO_{1-2}R^{12}$;

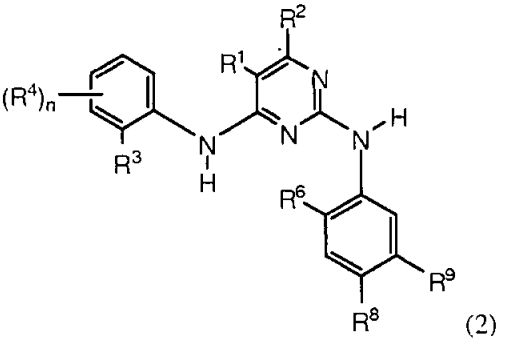
R^{12} and R^{13} are independently an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, or a 5-7 membered heterocyclic ring comprising N, O and/or S; aryl or heteroaryl; or R^{12} is H, C_{1-6} alkyl;

X is $(CR_2)_qY$, cyano, $CO_{1-2}R^{12}$, $CONR(R^{12})$, $CONR(CR_2)_pNR(R^{12})$, $CONR(CR_2)_pOR^{12}$, $CONR(CR_2)_pSR^{12}$, $CONR(CR_2)_pS(O)_{1-2}R^{12}$ or $(CR_2)_{1-6}NR(CR_2)_pOR^{12}$;

Y is an optionally substituted 3-12 membered carbocyclic ring, a 5-12 membered aryl, or a 5-12 membered heteroaryl or heterocyclic ring comprising N, O and/or S and attached to A^2 or A^3 or both via a carbon atom of said heteroaryl or heterocyclic ring when q in $(CR_2)_qY$ is 0; and

n, p and q are independently 0-4.

[0032] In one embodiment, the invention provides compounds having Formula (2):



(2)

wherein R^1 is halo or C_{1-6} alkyl;

R^2 is H; or

R^1 and R^2 together form an optionally substituted 5-6 membered heteroaryl or heterocyclic ring comprising one or two nitrogen atoms;

R^6 is isopropoxy or methoxy;

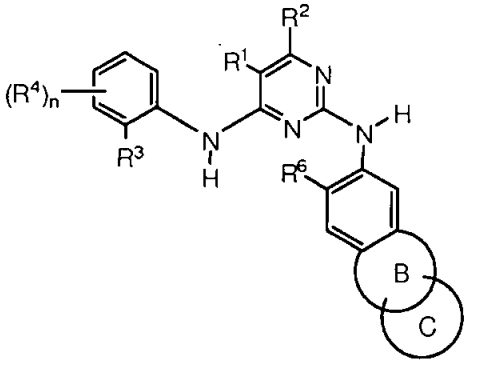
one of R^8 and R^9 is $(CR_2)_qY$ and the other is C_{1-6} alkyl, cyano, $CO_{1-2}R^{12}$, $CONR(R^{12})$ or $CONR(CR_2)_pNR(R^{12})$;

Y is an optionally substituted C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, or phenyl; or Y is pyridyl, pyrazolyl, isoxazolyl, imidazolyl, thiazolyl, benzimidazolyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, azetidinyl, heptamethyleneimine or octamethyleneimine, each of which is attached to the phenyl ring via a carbon atom when q in $(CR_2)_qY$ is 0;

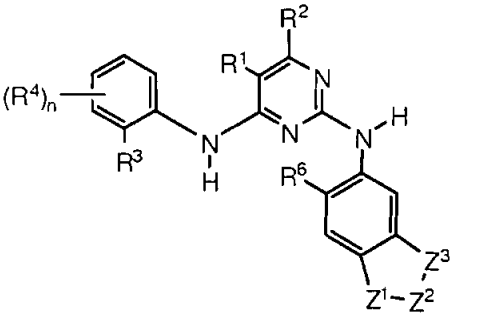
n is 0-1; and

q is 0-4.

[0033] In another embodiment, the invention provides compounds having Formula (3A) or (3B):

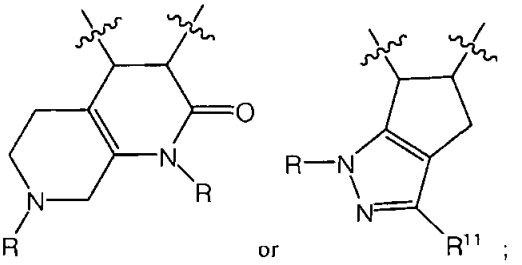


(3A)



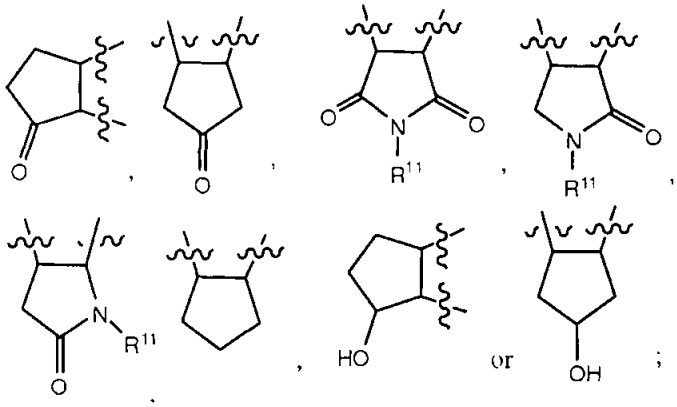
(3B)

wherein B and C together form



or ;

Z^1, Z^2 and Z^3 together form



or tautomers thereof;

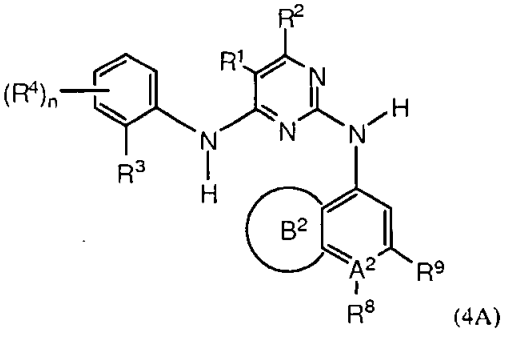
R^1 is halo or C_{1-6} alkyl;

R^2 is H; or

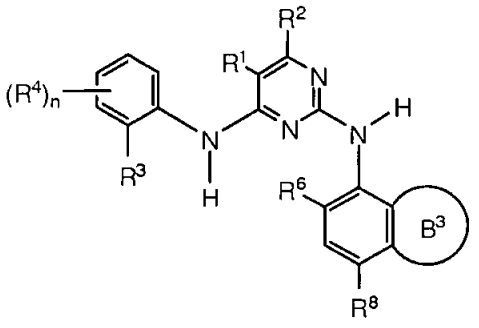
R^1 and R^2 together form an optionally substituted 5-7 membered carbocyclic ring, aryl, or heteroaryl or heterocyclic ring comprising N, O and/or S; and

R^6 is isopropoxy or methoxy.

[0034] In yet another embodiment, the invention provides compounds having Formula (4A) or Formula (4B):



(4A)



(4B);

wherein R^1 is halo or C_{1-6} alkyl;

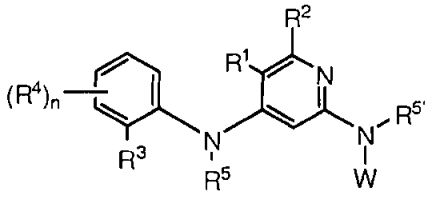
R^2 is H; or

R^1 and R^2 together form an optionally substituted 5-7 membered carbocyclic ring, aryl, or heteroaryl or heterocyclic ring comprising N, O and/or S;

R^6 is isopropoxy or methoxy; and

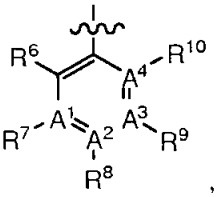
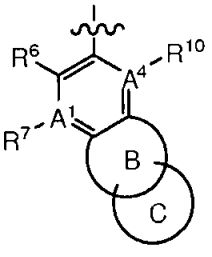
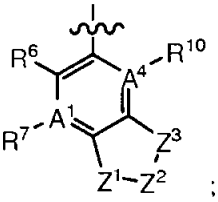
B^2 and B^3 are independently an optionally substituted 5-6 membered aryl or heteroaryl containing N, O or S.

[0035] In another aspect, the invention provides compounds having Formula (5):



(5)

or pharmaceutically acceptable salts thereof; wherein

W is  ,  or  ;

A^1 and A^4 are independently C or N;

each A^2 and A^3 is C, or one of A^2 and A^3 is N when R^6 and R^7 form a ring;

B and C are independently an optionally substituted 5-7 membered carbocyclic ring, aryl, heteroaryl or heterocyclic ring containing N, O or S;

Z^1, Z^2 and Z^3 are independently NR^{11}, C=O, CR-OR, $(CR_2)_{1-2}$ or =C-R^{12};

R^1 and R^2 are independently halo, OR^{12}, $NR(R^{12})$, SR^{12}, or an optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; or one of R^1 and R^2 is H;

R^3 is $(CR_2)_{0-2}SO_2R^{12}$, $(CR_2)_{0-2}SO_2NRR^{12}$, $(CR_2)_{0-2}CO_{1-2}R^{12}$, $(CR_2)_{0-2}CONRR^{12}$ or cyano;

R^4, R^6, and R^7 and R^{10} when attached to a carbon atom, are independently H, an optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; OR^{12}, $NR(R^{12})$, halo, nitro, SO_2R^{12}, $(CR_2)_pR^{13}$ or X; provided R^6 and R^7 are not both H;

R, R^5 and $R^{5'}$ are independently H or C_{1-6} alkyl;

R^8 and R^9 are independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo or X, or one of R^8 and R^9 is H; and provided one of R^8 and R^9 is X;

alternatively, R^1 and R^2, or R^6 and R^7, R^7 and R^8, or R^9 and R^{10}, when attached to a carbon atom may form an optionally substituted 5-7 membered monocyclic or fused carbocyclic ring, aryl, or heteroaryl or heterocyclic ring comprising N, O and/or S; or R^7, R^8, R^9 and R^{10} are absent when attached to N;

R^{11} is H, C_{1-6} alkyl, C_{2-6} alkenyl, $(CR_2)_pCO_{1-2}R$, $(CR_2)_pOR$, $(CR_2)_pR^{13}$, $(CR_2)_pNRR^{12}$, $(CR_2)_pCONRR^{12}$ or $(CR_2)_pSO_{1-2}R^{12}$;

R^{12} and R^{13} are independently an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, or a 5-7 membered heterocyclic ring comprising N, O and/or S; aryl or heteroaryl; or R^{12} is H, C_{1-6} alkyl;

X is $(CR_2)_qY$. cyano, $CO_{1-2}R^{12}$, $CONR(R^{12})$, $CONR(CR_2)_pNR(R^{12})$, $CONR(CR_2)_pOR^{12}$, $CONR(CR_2)_pSR^{12}$, $CONR(CR_2)_pS(O)_{1-2}R^{12}$ or $(CR_2)_{1-6}NR(CR_2)_pOR^{12}$;

Y is an optionally substituted 3-12 membered carbocyclic ring, a 5-12 membered aryl, or a 5-12 membered heteroaryl or heterocyclic ring comprising N, O and/or S and attached to A^2 or A^3 or both via a carbon atom of said heteroaryl or heterocyclic ring when q in $(CR_2)_qY$ is 0; and

n, p and q are independently 0-4.

[0036] In each of the above formula, Y or R^{13} may independently be heterocyclic rings, which may be a bicyclic amine or bicyclic diamine. Examples of bicyclic amine and bicyclic diamines include but are not limited to an optionally substituted hexanemethyleneimine; heptamethyleneimine; quinuclidine; 3-azabicyclo(3,3,0)octane; 3,8-diazabicyclo[3,2,1]octane; octahydro-1H-pyrido[3,4-C]azepine; octahydropyrrolizine; 6-azabicyclo[3,2,1]octane; 3-azabicyclo[3,2,1]octane; 2,5-diazabicyclo[2,2,1]heptane; 1-azabicyclo[2,2,1]heptane; 2-azabicyclo[2,2,1]heptane; 1,4-diazabicyclo[4,4,0]decane; 1,4-diazabicyclo[4,3,0]nonane; 1-azabicyclo[3,2,1]octane; 3-azabicyclo[3,3,0]octane; 8-azabicyclo[3,2,1]octane; 3,9-

diazabicyclo[4.2.1]nonane; octahydropyrrolo[3,4-C]pyrrole; octahydropyrrolo[3,4-B]pyrrole; hexahydropyrrolo[3,2-B]pyrrole; hexahydropyrrolo[3,2-C]pyrrole; 1,4-diazacyclooctane; 1,5-diazacyclooctane; 3,7-diazabicyclo[4,2,0]octane; 3,7-diazabicyclo[3,3,1]nonane; octahydropyrrolo[3,4-C]pyridine; octahydropyrrolo[3,4-B]pyridine; octahydrocyclopenta[C]pyrrolidine; hexahydrocyclopenta[C]pyrrolidine; 8-azabicyclo[3,2,1]octane; decahydroquinoline; decahydroisoquinoline; decahydropyrido[3,4-B]azepine; decahydropyrido[4,3-B]azepine; 9-azabicyclo[3,3,1]nonane; bispidine; 3-azabicyclo[3,1,0]hexane; 8-azabicyclo[3,2,1]octane; 2-azabicyclo[3.3.1]nonane; tetrahydroquinoline; tetrahydroisoquinoline; 2,5-diazabicyclo[2,2,2]octane; decahydro-2,7-naphthyridine; 1,4-diazepane; azonane; octahydro-1H-indole; octahydro-1H-isoindole; 2-azabicyclo[3,3,0]octane; 6-azabicyclo[3,2,1]octane; 7-aza-bicyclo[2.2.1]heptane; decahydropyrazino[1,2-a]azepine; 3,8-diaza-bicyclo[3,2,1]octane; 3-azabicyclo[3,2,1]octane; 3-aza-tricyclo[4,2,1,0(2,5)]nonane; 2,6-diazaspiro[3,5]nonane; 6-azabicyclo[2,1,0]hexane, etc.

[0037] In each of the above formula, any asymmetric carbon atoms may be present in the (R)-. (S)-or (R,S)-configuration. The compounds may thus be present as mixtures of isomers or as pure isomers, for example, as pure enantiomers or diastereomers. The invention further encompasses possible tautomers of the inventive compounds.

[0038] In each of the above formula, each optionally substituted moiety may be substituted with C_{1-6} alkyl, C_{2-6} alkenyl or C_{3-6} alkynyl, each of which may be optionally halogenated or optionally having a carbon that may be replaced or substituted with N, S, O, or a combination thereof (for example, hydroxylC_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl); halo, amino, amidino, C_{1-6} alkoxy; hydroxyl, methylenedioxy, carboxy; C_{1-8} alkylcarbonyl, C_{1-8} alkoxycarbonyl, carbamoyl, C_{1-8} alkylcarbamoyl, sulfamoyl, cyano, oxo, nitro, or an optionally substituted carbocyclic ring, heterocyclic ring, aryl or heteroaryl as previously described.

Pharmacology and Utility

[0039] The compounds of the invention and their pharmaceutically acceptable salts exhibit valuable pharmacological properties when tested in vitro in cell-free kinase assays and in cellular assays, and are therefore useful as pharmaceuticals.

[0040] In one aspect, compounds of Formula (1), (2), (3A), (3B), (4A), (4B) or (5) may inhibit the tyrosine kinase activity of anaplastic lymphoma kinase (ALK) and the fusion protein of NPM-ALK. This protein tyrosine kinase results from a gene fusion of nucleophosmin (NPM)

and ALK, rendering the protein tyrosine kinase activity of ALK ligand independent. NPM-ALK plays a key role in signal transmission in a number of hematopoetic and other human cells leading to hematological and neoplastic diseases, for example in anaplastic large-cell lymphoma (ALCL) and non-Hodgkin's lymphomas (NHL), specifically in ALK+NHL or Alkomas, in inflammatory myofibroblastic tumors (IMT) and neuroblastomas. (Duyster et al. 2001 Oncogene 20, 5623-5637). In addition to NPM-ALK, other gene fusions have been identified in human hematological and neoplastic diseases; for example, TPM3-ALK (a fusion of nonmuscle tropomyosin with ALK).

[0041] The inhibition of ALK tyrosine kinase activity may be 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 are 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 are incubated for 10 min at ambient temperature. Reactions are 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 min with H_2O. Following washing (0.5 % H_3PO_4), plates are counted in a liquid scintillation counter. IC_{50} values are calculated by linear regression analysis of the percentage inhibition.

[0042] Compounds of Formula (1), (2), (3A), (3B), (4A), (4B) or (5) may potently inhibit the growth of human NPM-ALK overexpressing murine BaF3 cells (DSMZ Deutsche Sammiung von Mikroorganismen und Zelikulturen GmbH, Germany). The expression of NPM-ALK may be 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 may result 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)).

[0043] The inhibitory activity of the compounds of the invention may be determined as follows. In general, BaF3-NPM-ALK cells (15,000/microtitre plate well) are transferred to 96-well microtitre plates. Test compounds dissolved in dimethyl sulfoxide (DMSO) are 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 are incubated for two days during which the control cultures without test compound are 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 min 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.

[0044] IC_{50} values may be determined by a computer-aided system using the formula:

$$IC_{50} = [(ABS_{test}\text{-}ABS_{start})/(ABS_{control}\text{-}ABS_{start})] \times 100. \text{ (ABS = absorption)}$$

[0045] 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. The compounds of the invention in free form or in pharmaceutically acceptable salt form, may exhibit valuable pharmacological properties, for example, as indicated by the *in vitro* tests described in this application. In general, compounds of the invention have IC_{50} values from 1 nM to 10 µM. In some examples, compounds of the invention have IC_{50} values from 0.01 µM to 5 µM. In other examples, compounds of the invention have IC_{50} values from 0.01 µM to 1 µM, or more particularly from 1 nM to 1 µM. In yet other examples, compounds of the invention have IC_{50} values of less than 1 nM or more than 10 µM. The compounds of the invention may exhibit a percentage inhibition of greater than 50%, or in other embodiments, may exhibit a percentage inhibition greater than about 70%, against ALK at 10 µM.

[0046] The antiproliferative action of the inventive compounds may also be 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 the invention may exhibit inhibitory activity with an IC_{50} in the range from approximately 0.01 to 1 μM. The action of the inventive compounds on autophosphorylation of the ALK may be 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).

[0047] In another aspect, the compounds of the invention may inhibit Focal Adhesion Kinase (FAK), and may be useful as pharmaceuticals to treat conditions caused by a malfunction of signal cascades connected with FAK, such as in the treatment of particular tumors. The inhibition of endogenous FAK signaling results in reduced motility, and in some cases induces cell death. On the other hand, enhancing FAK signaling by exogenous expression increases cell motility. In addition, FAK is overexpressed in invasive and metastatic epithelial, mesenchymal, thyroid and prostate cancers. Consequently, an inhibitor of FAK is likely to be a drug for anti-tumor growth and metastasis. The compounds of the invention may thus be useful to prevent and/or treat a vertebrate and more particularly a mammal, affected by a neoplastic disease, in particular breast tumor, cancer of the bowel (colon and rectum), stomach cancer and cancer of the ovary and prostate, non-small cell lung cancer, small cell lung cancer, cancer of liver, melanoma, bladder tumor and cancer of head and neck.

[0048] The relation between FAK inhibition and immuno-system is described e.g. in G.A. van Seventer et al., Eur. J. Immunol. 2001, 31, 1417-1427. Therefore, the compounds of the invention are, for example, useful to prevent and/or treat a vertebrate and more particularly a mammal, affected by immune system disorders, diseases or disorders mediated by T lymphocytes, B lymphocytes, mast cells and/or eosinophils e.g. acute or chronic rejection of organ or tissue allo-or xenografts, atherosclerosis, vascular occlusion due to vascular injury such as angioplasty, restenosis, hypertension, heart failure, chronic obstructive pulmonary disease, CNS disease such as Alzheimer disease or amyotrophic lateral sclerosis; cancer; infectious disease such as AIDS; septic shock or adult respiratory distress syndrome, ischemia/reperfusion injury e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, or traumatic shock.

[0049] In yet another aspect, the compounds of the invention may inhibit zeta chain-associate protein 70 (ZAP-70). ZAP-70 protein tyrosine kinase interaction of the agents of the invention may be demonstrated, for example, by their ability to prevent phosphorylation of

LAT-11 (linker for activation of T cell) by human ZAP-70 protein tyrosine kinase in aqueous solution. Therefore, the compounds of the invention may be useful for the prevention or treatment of disorders or diseases where ZAP-70 inhibition plays a role.

[0050] The compounds of the invention may also inhibit insulin like growth-factor receptor 1 (IGF-1R), and may be useful in the treatment of IGF-1 R mediated diseases. Examples of IGF-1R mediated diseases include but are not limited to proliferative diseases, such as tumors, for example breast, renal, prostate, colorectal, thyroid, ovarian, pancreas, neuronal, lung, uterine and gastro intestinal tumors, as well as osteosarcomas and melanomas. The efficacy of the compounds of the invention as inhibitors of IGF-1R tyrosine kinase activity may be demonstrated using a cellular capture ELISA. In this assay, the activity of the compounds of the invention against (IGF-1)-induced autophosphorylation of the IGF-1R is determined.

[0051] The compounds of the invention may also be useful in the treatment and/or prevention of acute or chronic inflammatory diseases or disorders or autoimmune diseases e.g. rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, diabetes (type I and II) and the disorders associated therewith, respiratory diseases such as asthma or inflammatory liver injury, inflammatory glomerular injury, cutaneous manifestations of immunologically-mediated disorders or illnesses, inflammatory and hyperproliferative skin diseases (such as psoriasis, atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis and further eczematous dermatitis, seborrhoeic dermatitis), s inflammatory eye diseases, e.g. Sjoegren's syndrome, keratoconjunctivitis or uveitis, inflammatory bowel disease, Crohn's disease or ulcerative colitis.

[0052] In accordance with the foregoing, the present invention provides:

(1) a compound of the invention for use as a pharmaceutical;

(2) a compound of the invention for use as an ALK inhibitor, FAK inhibitor, ZAP-70 inhibitor and/or IGF-1R inhibitor, for example for use in any of the particular indications hereinbefore set forth;

(3) a pharmaceutical composition, e.g. for use in any of the indications herein before set forth, comprising a compound of the invention as active ingredient together with one or more pharmaceutically acceptable diluents or carriers;

(4) a method for the treatment of any particular indication set forth hereinbefore in a subject in need thereof which comprises administering an effective amount of a compound of the invention or a pharmaceutical composition comprising same;

(5) the use of a compound of the invention for the manufacture of a medicament for the treatment or prevention of a disease or condition in which ALK, FAK, ZAP-70 and/or IGF-1R activation plays a role or is implicated;

(6) the method as defined above under (4) comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of the invention and one or more further drug substances, said further drug substance being useful in any of the particular indications set forth hereinbefore;

(7) a combination comprising a therapeutically effective amount of a compound of the invention and one or more further drug substances, said further drug substance being useful in any of the particular indications set forth hereinbefore;

(8) use of a compound of the invention for the manufacture of a medicament for the treatment or prevention of a disease which responds to inhibition of the anaplastic lymphoma kinase;

(9) the use according to (8), wherein the disease to be treated is selected from anaplastic large cell lymphoma, non-Hodgkin's lymphomas, inflammatory myofibroblastic tumors, neuroblastomas and neoplastic diseases;

(10) the use according to (8) or (9), wherein the compound is or a pharmaceutically acceptable; salt of any one of the examples;

(11) a method for the treatment of a disease which responds to inhibition of the anaplastic lymphoma kinase, especially a disease selected from anaplastic large-cell lymphoma, non Hodgkin's lymphomas, inflammatory myofibroblastic tumors, neuroblastomas and neoplastic diseases, comprising administering an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof.

Administration and Pharmaceutical Compositions

[0053] In general, compounds of the invention will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors known to those of ordinary skill in the art. For example, for the treatment of neoplastic diseases and immune system disorders, the required

dosage will also vary depending on the mode of administration, the particular condition to be treated and the effect desired.

[0054] In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.01 to about 100 mg/kg per body weight, or particularly, from about 0.03 to 2.5 mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, may be in the range from about 0.5 mg to about 2000 mg, or more particularly, from about 0.5 mg to about 100 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50 mg active ingredient.

[0055] Compounds of the invention may be administered as pharmaceutical compositions by any conventional route; for example, enterally, e.g., orally, e.g., in the form of tablets or capsules; parenterally, e.g., in the form of injectable solutions or suspensions; or topically, e.g., in the form of lotions, gels, ointments or creams, or in a nasal or suppository form.

[0056] Pharmaceutical compositions comprising a compound of the present invention in free form or in a pharmaceutically acceptable salt form in association with at least one pharmaceutically acceptable carrier or diluent may be manufactured in a conventional manner by mixing, granulating, coating, dissolving or lyophilizing processes. For example, pharmaceutical compositions comprising a compound of the invention in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent. Unit dosage forms for oral administration contain, for example, from about 0.1 mg to about 500 mg of active substance.

[0057] In one embodiment, the pharmaceutical compositions are solutions of the active ingredient, including suspensions or dispersions, such as isotonic aqueous solutions. In the case of lyophilized compositions comprising the active ingredient alone or together with a carrier such as mannitol, dispersions or suspensions can be made up before use. The pharmaceutical compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. Suitable preservatives include but are not limited to antioxidants such as ascorbic acid, or microbicides, such as sorbic acid or benzoic acid. The solutions or suspensions may further comprise viscosity-increasing agents, including but not limited to, sodium

carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone, gelatins, or solubilizers, e.g. Tween 80 (polyoxyethylene(20)sorbitan mono-oleate).

[0058] Suspensions in oil may comprise as the oil component the vegetable, synthetic, or semi-synthetic oils customary for injection purposes. Examples include liquid fatty acid esters that contain as the acid component a long-chained fatty acid having from 8 to 22 carbon atoms, or in some embodiments, from 12 to 22 carbon atoms. Suitable liquid fatty acid esters include but are not limited to lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brassidic acid and linoleic acid, and if desired, may contain antioxidants, for example vitamin E, 3-carotene or 3,5-di-tert-butyl-hydroxytoluene. The alcohol component of these fatty acid esters may have six carbon atoms and may be monovalent or polyvalent, for example a mono-, di- or trivalent, alcohol. Suitable alcohol components include but are not limited to methanol, ethanol, propanol, butanol or pentanol or isomers thereof; glycol and glycerol.

[0059] Other suitable fatty acid esters include but are not limited ethyl-oleate, isopropyl myristate. isopropyl palmitate, LABRAFIL® M 2375, (polyoxyethylene glycerol), LABRAFIL® M 1944 CS (unsaturated polyglycolized glycerides prepared by alcoholysis of apricot kernel oil and comprising glycerides and polyethylene glycol ester), LABRASOL™ (saturated polyglycolized glycerides prepared by alcoholysis of TCM and comprising glycerides and polyethylene glycol ester; all available from GaKefosse, France), and/or MIGLYOL® 812 (triglyceride of saturated fatty acids of chain length C_8 to C_{12} from Hüls AG. Germany), and vegetable oils such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil, or groundnut oil.

[0060] Pharmaceutical compositions for oral administration may be obtained, for example, by combining the active ingredient with one or more solid carriers, and if desired, granulating a resulting mixture. and processing the mixture or granules by the inclusion of additional excipients, to form tablets or tablet cores.

[0061] Suitable carriers include but are not limited to fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations, and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starches. for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone, and/or, if

desired, disintegrators, such as the above-mentioned starches, carboxymethyl starch, crosslinked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients include flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

[0062] Tablet cores may be provided with suitable, optionally enteric, coatings through the use of, inter alia, concentrated sugar solutions which may comprise gum arable, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or tablet coatings, for example for identification purposes or to indicate different doses of active ingredient.

[0063] Pharmaceutical compositions for oral administration may also include hard capsules comprising gelatin or soft-sealed capsules comprising gelatin and a plasticizer, such as glycerol or sorbitol. The hard capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders, and/or glidants, such as talc or magnesium stearate, and optionally stabilizers. In soft capsules, the active ingredient may be dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene or propylene glycol, to which stabilizers and detergents, for example of the polyoxyethylene sorbitan fatty acid ester type, may also be added.

[0064] Pharmaceutical compositions suitable for rectal administration are, for example, suppositories comprising a combination of the active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

[0065] Pharmaceutical compositions suitable for parenteral administration may comprise aqueous solutions of an active ingredient in water-soluble form, for example of a water-soluble salt, or aqueous injection suspensions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilizers. The active ingredient, optionally together with excipients, can also be in the form of a lyophilizate and can be made into a solution before parenteral administration by the addition of suitable solvents. Solutions such as are used, for example, for parenteral administration can also be employed as

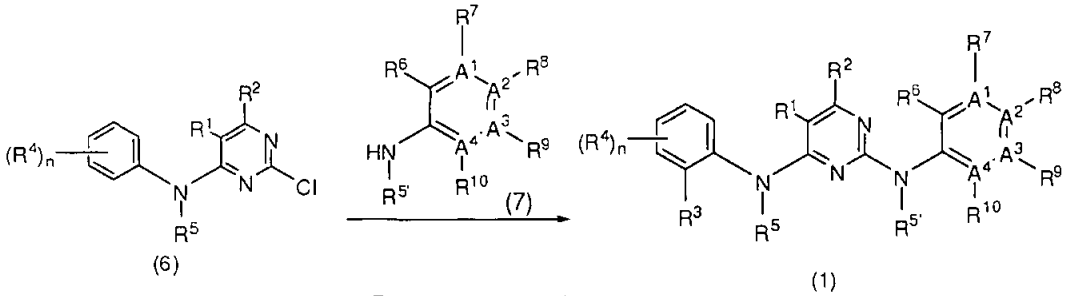
infusion solutions. The manufacture of injectable preparations is usually carried out under sterile conditions, as is the filling, for example, into ampoules or vials, and the sealing of the containers.

[0066] The compounds of the invention may be administered as the sole active ingredient, or together with other drugs useful against neoplastic diseases or useful in immunomodulating regimens. For example, the compounds of the invention may be used in accordance with the invention in combination with pharmaceutical compositions effective in various diseases as described above, e.g. with cyclophosphamide, 5-fluorouracil, fludarabine, gemcitabine, cisplatinum, carboplatin, vincristine, vinblastine, etoposide, irinotecan, paclitaxel, docetaxel, rituxan, doxorubicine, gefitinib, or imatinib; or also with cyclosporins, rapamycins, ascomycins or their immunosuppressive analogs, e.g. cyclosporin A, cyclosporin G, FK-506, sirolimus or everolimus, corticosteroids, e.g. prednisone, cyclophosphamide, azathioprene, methotrexate, gold salts, sulfasalazine, antimalarials, brequinar, leflunomide, mizoribine, mycophenolic acid, mycophenolate, mofetil, 15-deoxyspergualine, immuno-suppressive monoclonal antibodies, e.g. monoclonal antibodies to leukocyte receptors, e.g. MHC, CD2, CD3, CD4, CD7, CD25, CD28, I CD40, CD45, CD58, CD80, CD86, CD152, CD137, CD154, ICOS, LFA-1, VLA-4 or their ligands, or other immunomodulatory compounds, e.g. CTLA41g.

[0067] The invention also provides for a pharmaceutical combinations, e.g. a kit, comprising a) a first agent which is a compound of the invention as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent. The kit can comprise instructions for its administration.

Processes for Making Compounds of the Invention

[0068] Compounds of Formula (1) may be prepared following Reaction Scheme I, in which each substituent is as defined in the Summary of the Invention:



Reaction Scheme I

[0069] A compound of Formula (1) may be synthesized by reacting a compound of formula (6) with a compound of formula (7) in the presence of palladium catalyst (for example palladium acetate and the like), ligand (for example xantphos and the like) and base (for example cesium carbonate and the like) in a suitable solvent (for example, THF, and the like). The reaction proceeds in a temperature range of about 70°C to about 180°C and can take 10 min. to 8 hours to complete.

[0070] Alternatively, a compound of Formula (1) may be synthesized by reacting a compound of formula (6) with a compound of formula (7) in the presence of acid (for example HCl, TsOH and the like), in a suitable solvent (for example, 2-propanol, and the like). The reaction proceeds in a temperature range of about 70°C to about 150°C and can take up to 12 hours to complete.

Additional Processes for Making Compounds of the Invention

[0071] The compounds of the invention, including their salts, are also obtainable in the form of hydrates, or their crystals may include for example the solvent used for crystallization (present as solvates). Salts can usually be converted to compounds in free form, e.g., by treating with suitable basic agents, for example with alkali metal carbonates, alkali metal hydrogen carbonates, or alkali metal hydroxides, such as potassium carbonate or sodium hydroxide. In view of the close relationship between the novel compounds in free form and those in the form of their salts, including those salts that may be used as intermediates, for example in the purification or identification of the novel compounds, any reference to the free compounds hereinbefore and hereinafter is to be understood as referring also to the corresponding salts, as appropriate.

[0072] Salts of the inventive compounds with a salt-forming group may be prepared in a manner known per se. Acid addition salts of compounds of Formula (1), (2), (3A), (3B), (4A), (4B) or (5) may thus be obtained by treatment with an acid or with a suitable anion exchange reagent. Pharmaceutically acceptable salts of the compounds of the invention may be formed, for example, as acid addition salts, with organic or inorganic acids, from compounds of Formula (1), (2), (3A), (3B), (4A), (4B) or (5) with a basic nitrogen atom.

[0073] Suitable inorganic acids include, but are not limited to, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids include, but are not limited to, carboxylic, phosphoric, sulfonic or sulfamic acids, for example acetic acid, propionic

acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid,-malic acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 4 aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane-or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disuifonic acid, 2-, 3-or 4 methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N cyclohexylsulfamic acid, N-methyl-, N-ethyl-or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

[0074] For isolation or purification purposes, it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable in the form of pharmaceutical preparations).

[0075] Compounds of the invention in unoxidized form may be prepared from N-oxides of compounds of the invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (e.g. acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

[0076] Prodrug derivatives of the compounds of the invention may be prepared by 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 may be prepared by reacting a non-derivatized compound of the invention with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

[0077] Protected derivatives of the compounds of the invention may be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal may be found in T. W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

[0078] Compounds of the invention may be 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. Resolution of enantiomers may be carried out using covalent diastereomeric derivatives of the compounds of the invention, or by using dissociable complexes (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and may be readily separated by taking advantage of these dissimilarities. The diastereomers may be separated by fractionated crystallization, 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 may be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981.

[0079] In summary, the compounds of the invention may be made by a process, which involves:

(a) that of Reaction Scheme I; and

(b) 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.

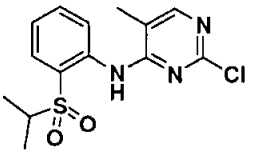
[0080] Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter. One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used. The present

invention is further exemplified, but not limited, by the following and Examples that illustrate the preparation of the compounds of the invention.

Preparation of Intermediates

Intermediate 1

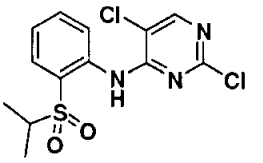
2-chloro-*N*-(2-(*iso*-propylsulfonyl)phenyl)-5-methylpyrimidin-4-amine



[0081] To a suspension of 730 mg of NaH in a mixture of DMF/DMSO (25/2.5 ml) is added drop-wise at 0°C, 2.53 g (12.69 mmol) of 2-(*iso*-propylsulfonyl)benzenamine in DMF/DMSO (10 ml, ratio 9/1). The solution is stirred 30 minutes at 0°C and 4.11 g (25.3 mmol, 2 eq.) of 2,4-dichloro-5-methylpyrimidine diluted in 10 ml of DMF/DMSO (ratio: 9/1) is added dropwise. The solution is warmed-up to room temperature and stirred overnight. After work-up, the crude product is directly crystallized from cold CH_3CN in several batches to afford 2-chloro-*N*-(2-(*iso*-propylsulfonyl)phenyl)-5-methylpyrimidin-4-amine as pale creamy colored crystals: ESMS *m/z* 326.1 ($M + H^+$).

Intermediate 2

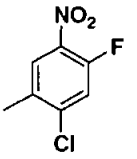
Synthesis of 2,5-dichloro-*N*-(2-(*iso*-propylsulfonyl)phenyl)pyrimidin-4-amine



[0082] Using the same procedure described for the synthesis of 2-chloro-*N*-(2-(*iso*-propylsulfonyl)phenyl)-5-methylpyrimidin-4-amine, 2,5-dichloro-*N*-(2-(*iso*-propylsulfonyl)phenyl)pyrimidin-4-amine is isolated as a creamy colored solid: ESMS *m/z* 346.0 ($M + H^+$).

Intermediate 3

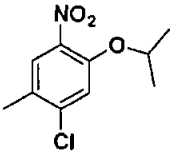
2-chloro-4-fluoro-5-nitrotoluene



[0083] To a solution of 100 g (0.7 mol) of 2-chloro-4-fluorotoluene in 250 ml of concentrated H_2SO_4 is added portion-wise 85 g (0.875 mol) of KNO_3 at 0°C (addition of the whole amount of KNO_3 is finished in about 1 hour). The reddish mixture is slowly warmed-up at room temperature overnight and quenched over crushed ice and extracted with EtOAc. The organic layers are combined, dried over $MgSO_4$ and concentrated. The crude oil is then purified over a large silica plug (eluent: 97/3 hexanes/EtOAc) to afford 2-chloro-4-fluoro-5-nitrotoluene as a pale yellow oil that solidifies upon standing. ^{1}H NMR ($CDCl_3$, 400 Mz): 7.97 (d, J = 8.0 Hz, 1H). 7.32 (d, J = 10.4 Hz, 1H), 2.43 (s, 3H).

Intermediate 4

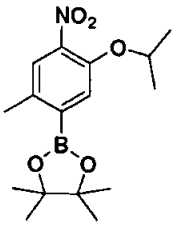
2-chloro-4-*iso*propoxy-5-nitrotoluene



[0084] To a solution of 25 g (0.131 mol) of 2-chloro-4-fluoro-5-nitrotoluene in 250 ml of 2-propanol is added 208 g (0.659 mol, 5 eq.) of Cs_2CO_3. The mixture is stirred at 60°C overnight and most of the 2-propanol is evaporated under reduced pressure. Water is added and the solution is extracted with EtOAc. The organic layers are combined, dried over $MgSO_4$, concentrated and the crude product filtrated over a silica plug (eluent: 95/5 hexanes/EtOAc) to afford 2-chloro-4-*iso*propoxy-5-nitrotoluene as a pale yellow fluffy solid.

Intermediate 5

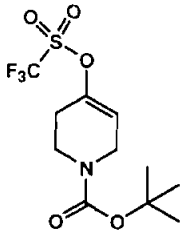
2-methyl-4-nitro-5-*iso*propoxy-phenylboronic acid pinacol ester



[0085] A mixture of 5.09 g 2-chloro-4-*iso*propoxy-5-nitrotoluene (0.02216 mol), 6.20 g (0.02437 mol) of pinacol diborane, 595 mg (0.00212 mol) of PCy_3, 1.014 g (0.00108 mol) of Pd_2dba_3 and 3.16 g (0.0322 mol) of KOAc in 100 ml of dry dioxane is heated to 100°C overnight. After cooling to RT, the dark solution is filtered over Celite and the solvent evaporated under reduced pressure. The crude oil is purified with silica gel column chromatography (eluent: 95/5 hexanes/EtOAc) to afford 2-methyl-4-nitro-5-*iso*propoxy-phenylboronic acid pinacol ester as an oil that solidifies upon standing. ^{1}H NMR ($CDCl_3$, 400 Mz): 7.51 (s, 1H), 7.44 (s, 1H), 4.70 (m, 1H), 2.48 (s, 3H), 1.36 (d, J = 7.6 Hz, 6H), 1.35 (s, 12H).

Intermediate 6

4-Trifluoromethanesulfonyloxy-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester

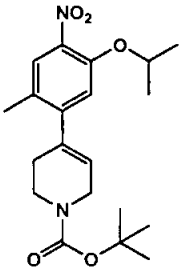


[0086] A solution of *N-tert*-Butoxycarbonyl-4-piperidone (10.17 g, 0.05 mol) in THF (100 mL) is added dropwise into a cooled (-78 °C), vigorously stirring solution of LDA (40 mL of 1.5 M solution in cyclohexanes, 0.06 mol) in THF (100 mL), under N_2. The reaction mixture is left at -78 °C for 30 min before adding a solution of phenyl trifluorosulfonimide (19.85 g, 0.055 mol) in THF (50 mL). Then the reaction mixture is warmed to room temperature and stirred for 3 h. The reaction is quenched at 0 °C with 100 mL of saturated aqueous NH_4Cl and filtered through Celite. The filtrate is added to 100 mL of EtOAc and the layers are separated. The organic layer is washed with H_2O, dried over $MgSO_4$ and concentrated. The crude product is purified by silica flash column chromatography (0-30% EtOAc in Hexanes as eluent and checked by TLC stained

with 2% of $KMnO_4$ in EtOH) to afford 4-Trifluoromethanesulfonyloxy-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester as a yellow oil.

Intermediate 7

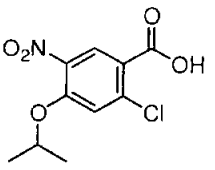
4-(5-Isopropoxy-2-methyl-4-nitro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester



[0087] To a solution of 2-methyl-4-nitro-5-*iso*propoxy-phenylboronic acid pinacol ester (2.04 g, 6.4 mmol) and 4-Trifluoromethanesulfonyloxy-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (3.2 g, 9.6 mmol) in 110 mL of DME/H_2O (10:1 V/V) is added $Pd(PPh_3)_4$ (365 mg, 0.32 mmol) and Cs_2CO_3 (4.2 g, 12.8 mmol). The reaction mixture is heated under N_2 at 80 °C overnight. After cooling to room temperature, the reaction is filtered through Celite and the filtrate is diluted with 100 mL of EtOAc, sequentially washed with H_2O, brine, and finally concentrated in vacuo. The crude product is purified by silica gel flash chromatography (5%-15% EtOAc in Hexanes as eluent) to afford 4-(5-Isopropoxy-2-methyl-4-nitro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester as a yellow oil. ^{1}H NMR (CD_3OD, 400 Mz): 7.59 (s, 1H), 6.96 (s, 1H), 5.67 (broad s, 1H), 4.73 (m, 1H), 4.06 (m, 2H), 3.65 (m, 2H), 2.37 (m, 2H), 2.25 (s, 3H), 1.50 (s, 9H), 1.33 (d, J = 6.0 Hz, 6H).

Intermediate 8

2-Chloro-4-isopropoxy-5-nitro-benzoic acid

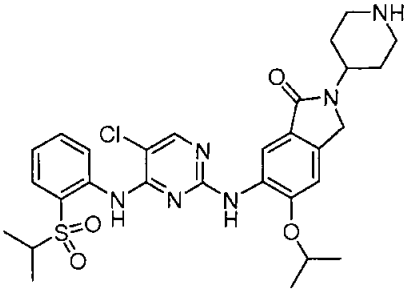


[0088] A mixture of 2-chloro-4-fluoro-5-nitro-benzoic acid (5.0 g, 22.8 mmol) and cesium carbonate (29.7 g, 91.1 mmol) in 2-propanol (100 mL) is heated at 50°C overnight. The solvent

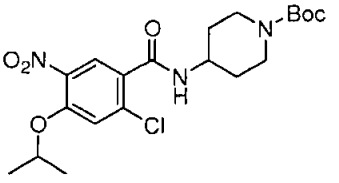
is removed *in vacuo* and 100 mL of water is added. Concentrated aqueous HCl is added dropwise to this solution at 0 °C until pH=2. The product precipitate which forms is isolated by filtration, washed by water and dried under vacuum to give 2-chloro-4-isopropoxy-5-nitro-benzoic acid.

Example 1

6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-piperidin-4-yl-2,3-dihydro-isoindol-1-one (**178**)

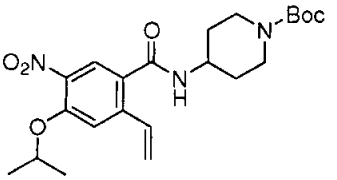


Steps 1 and 2: 4-(2-Chloro-4-isopropoxy-5-nitro-benzoylamino)-piperidine-1-carboxylic acid tert-butyl ester



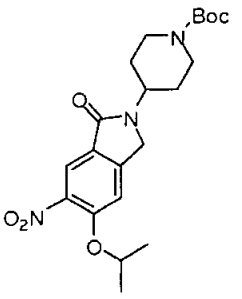
[0089] To a solution of 2-chloro-4-isopropoxy-5-nitro-benzoic acid (**Intermediate 8,** 10 g, 38.5 mmol) in DCM (200 mL) and DMF (1mL), is slowly added thionyl chloride (9.17 g, 77 mmol) via a syringe. The mixture is stirred for 3 hours, and is then concentrated to dryness. The obtained white solid, 2-chloro-4-isopropoxy-5-nitro-benzoyl chloride, is dried under vacuum. To a mixture of 4-amino-piperidine-1-carboxylic acid tert-butyl ester (1.44g, 7.2 mmol) and triethylamine (3 mL, 21.6 mmol) in DCM (100 mL), is slowly added 2-chloro-4-isopropoxy-5-nitro-benzoyl chloride (2g, 7.2 mmol) dissolved in DCM (10 mL) via syringe. The mixture is stirred at room temperature for 3 hours, and then is concentrated. The obtained solid is dissolved in ethyl acetate and is washed with water and brine respectively. After evaporation of the solvent, the title compound is obtained as light yellow solid, and is directly used for the next step without further purification.

Step 3: 4-(4-Isopropoxy-5-nitro-2-vinyl-benzoylamino)-piperidine-1-carboxylic acid tert-butyl ester



[0090] To a mixture of 4-(2-chloro-4-isopropoxy-5-nitro-benzoylamino)-piperidine-1-carboxylic acid tert-butyl ester (7.2 mmol) obtained in the previous step, vinylboronic acid dibutyl ester (1.72 g, 9.4 mmol) and sodium carbonate (5.34 g, 50.4 mmol) in THF/H_2O (100/25 mL) is added dichlorobis(triphenylphospine) palladium (II) (442 mg, 5% mmol). The mixture is purged with N_2 for 3 min and heated at 90°C under N_2 for overnight in a round bottom flask equipped with a condenser. The mixture is cooled to room temperature and poured into saturated aqueous ammonia chloride solution. The mixture is extracted with ethyl acetate (3 x 100 mL). The organic extracts are combined, washed with brine and concentrated. The crude product is purified with silica gel column chromatography (40% ethyl acetate in hexanes) to afford 4-(4-isopropoxy-5-nitro-2-vinyl-benzoylamino)-piperidine-1-carboxylic acid tert-butyl ester as white solid.

Steps 4, 5 and 6: 4-(5-Isopropoxy-6-nitro-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester



[0091] 4-(4-Isopropoxy-5-nitro-2-vinyl-benzoylamino)-piperidine-1-carboxylic acid tert-butyl ester obtained from previous step (1.9 g, 4.38mmol) is dissolved in DCM (100 mL) and is cooled to -78 °C. O_3 (g) is bubbled into the solution until the solution's color turns blue/gray. The solution is then purged with N_2 (g) until the blue color disappears. The solution is warmed to room temperature and treated with triphenyl phosphine resin (5 g) pre-swelled in DCM (100

mL). After 30 min, the mixture is filtered, the filtrate is concentrated, and the resulting residue dissolved in DCM/TFA (100mL / 25 mL). To this mixture is added triethyl silane (4.6 mL, 17.5 mmol). The resulting mixture is stirred at room temperature overnight. The reaction mixture is concentrated and re-dissolved in DCM. The DCM solution is washed with 1N aqueous HCl (3 x 20 mL). The combined aqueous layer is treated with conc. aqueous NaOH until pH =12. The aqueous layer is extracted with ethyl acetate (3 x 30 mL). The combined organic layers are washed with brine, and dried over sodium sulfate. A light yellow solid is obtained after evaporation of the organic solvent.

[0092] The solid is dissolved in a mixture of methanol and triethylamine (100mL, 9:1 v/v). To this mixture is added di-tert-butyl dicarbonate (680 mg, 3.1mmol). After stirring at 50 °C for 30 minutes, the mixture is concentrated and purified by silica gel flash column chromatography (eluent: 40~50% ethyl acetate in hexanes) to afford 4-(5-Isopropoxy-6-nitro-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.11 (s, 1H), 4.74 (q, 1H), 4.45-4.38 (m, 1H), 4.35 (s, 2H), 2.90-2.80 (m, 2H), 1.85-1.81 (m, 2H), 1.66-1.63 (m, 2H), 1.48 (s, 9H), 1.42 (d, 6H).

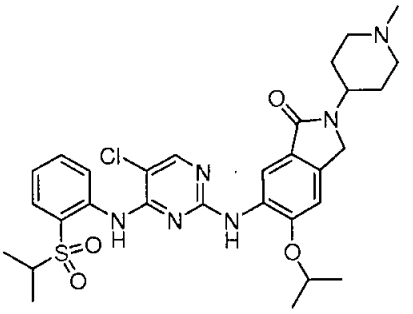
Steps 7, 8 and 9

[0093] To a solution of 4-(5-isopropoxy-6-nitro-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester from the previous step (850 mg, 2mmol) in methanol, is added Pd/C (10% on carbon, 100 mg). The mixture is hydrogenated under 1 atm of hydrogen gas. After 4 hours, the mixture is filtered and concentrated. The obtained aniline, as yellow solid, is used for next step without additional purification. To a mixture of the crude product (2 mmol) from previous step, (2,5-dichloro-pyrimidin-4-yl)-[2-(propane-2-sulfonyl)-phenyl]-amine (**Intermediate 2,** 770mg, 2.2 mmol), cesium carbonate (1.3g, 4mmol), and xantphos (115 mg, 0.2mmol) in THF (20 mL), is added palladium acetate (22mg, 5% mmol) in a microwave tube. The mixture is purged with N_2 for 3 min. The sealed tube is heated at 150°C for 20 min under microwave irradiation. The mixture is cooled, filtered and concentrated. The residue is purified by silica gel flash column chromatography (eluent: 65% ethyl acetate in hexanes) to afford a yellow solid. The solid is treated with DCM/TFA (1/1, 10mL) for 1 hour followed by concentration under vacuum. Final purification using preparative RP LC-MS affords 6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-piperidin-4-yl-2,3-dihydro-isoindol-1-one (**178**) as a white solid. ^{1}H NMR (400

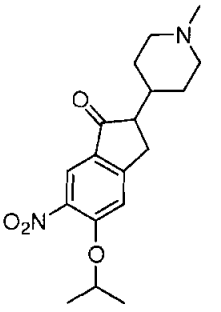
MHz. $CDCl_3$) δ 10.38 (s, 1H), 10.13 (s, 1H), 9.60-9.50 (br, 1H), 9.34-9.21 (br, 1H), 8.46 (d, 1H), 8.26 (s, 1H), 8.08 (s, 1H), 7.91 (dd, 1H), 7.71 (m, 1H), 7.34 (t, 1H), 7.03 (s, 1H), 4.30 (m, 1H), 4.53 (m, 1H), 4.33 (s, 2H), 3.62 (m, 2H), 3.21-3.09 (m, 3H), 2.31-2.21 (m, 2H), 2.09-2.05 (m, 2H), 1.41 (d, 6H), 2.30 (d, 6H); ESMS *m/z* 599.2 ($M + H^+$).

Example 2

6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-(1-methyl-piperidin-4-yl)-2,3-dihydro-isoindol-1-one (**181**)



Step 1: 5-Isopropoxy-2-(1-methyl-piperidin-4-yl)-6-nitro-indan-1-one



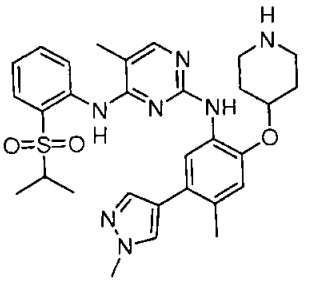
[0094] To a solution of 5-isopropoxy-6-nitro-2-piperidin-4-yl-indan-1-one (**Example 1, Step 5**) in THF (5 mL) and methanol (5 mL) is added formaldehyde (104.2 uL, 1.39 mmol) and 10 drops of AcOH sequentially. The reaction mixture is stirred at room temperature for 1h, then sodium cyanoborohydride (175.1 mg, 2.78 mmol) is added in one portion, and the reaction is stirred for an additional 30 min. The reaction is quenched by saturated aqueous NH_4Cl and concentrated *in vacuo* to give an oily residue. This oil is partitioned between EtOAc and brine, the organic extract is dried over Na_2SO_4, filtered and concentrated under vacuum. Silica gel chromatography (5% MeOH in DCM) affords 5-isopropoxy-2-(1-methyl-piperidin-4-yl)-6-nitro-indan-1-one; MS m/z 333.2 (M+1).

Steps 2 and 3

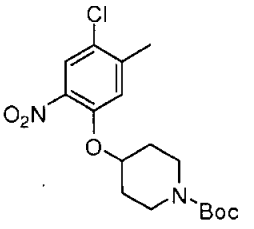
[0095] Following the procedures previously described **(Example 1, Steps 7 and 8)** using the product from Step 1 generates the title compound 6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-(1-methyl-piperidin-4-yl)-2,3-dihydro-isoindol-1-one (**181**) as a white solid. ^{1}H NMR 400 MHz (DMSO-d_6 with trace D_2O) δ 8.46 (d, 1H), 8.35 (s, 1H), 8.09(s, 1H), 7.82(d, 1H), 7.74(t, 1H), 7.36(t,1H), 7.33(s, 1H). 4.75 (m, 1H), 4.41(s, 2H), 4.29(m, 1H), 3.65(m, 2H), 3.44(m. 1H), 3.17(t, 2H), 2,79(s, 3H), 2.07(m, 2H), 1.98(d, 2H), 1.28(d, 6H), 1.14(d, 6H); MS m/z 613 (M+1).

Example 3

5-Methyl-N^2-[4-methyl-5-(1-methyl-1H-pyrazol-4-yl)-2-(piperidin-4-yloxy)-phenyl]-N^4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (**35**)



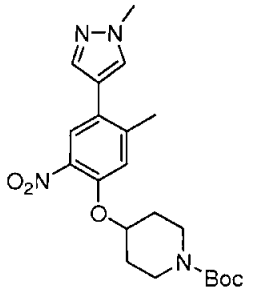
Step 1: 4-(4-Chloro-5-methyl-2-nitro-phenoxy)-piperidine-1-carboxylic acid tert-butyl ester



[0096] To a mixture of 4-Chloro-5-methyl-2-nitro-phenol (3.752 g, 20.0 mmol), 4-Hydroxy-piperidine-1-carboxylic acid tert-butyl ester (4.83 g, 24 mmol), and triphenylphosphine (6.23 g, 24 mmol) in 75 mL THF is added diisopropyl asodicarboxylate (4.73 mL, 245 mmol) in several portions at 22 °C for 1 h. The reaction is stirred at the same temperature for an additional 2 hrs. The reaction mixture is concentrated in vacuo. The residue is taken up in 50 mL ether, and let stand at 22 °C for 14 hrs. The resulting crystals are removed by filtration. The filtrate is

concentrated in vacuo, and the residue is purified over a 330 g SiO_2 column (ISCO) using a gradient of 20 to 40% ethyl acetate in hexanes as eluent, affording 4-(4-Chloro-5-methyl-2-nitro-phenoxy)-piperidine-1-carboxylic acid tert-butyl ester as dark yellow viscous oil. MS (ES+): 315.1 (MH+ - C4H8), 393.1 (MNa+).

Step 2: 4-[5-Methyl-4-(1-methyl-1H-pyrazol-4-yl)-2-nitro-phenoxy]-piperidine-1-carboxylic acid tert-butyl ester



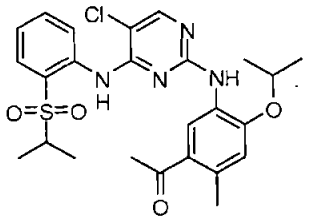
[0097] A mixture of 4-(4-Chloro-5-methyl-2-nitro-phenoxy)-piperidine-1-carboxylic acid tert-butyl ester from the previous step (375.8 mg, 1.01 mmol), 1-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (Boron Molecular, 224.4 mg 1.08 mmol), potassium phosphate tribasic monohydrate (392 mg), $Pd_2(dba)_3$ (45 mg), and dicyclophosphinobiphenyl (43 mg) in 4 mL of 1,4-dioxane/H_2O (3/1) is heated in a sealed tube at 150 °C for 20 min under microwave radiation. The reaction mixture is filtered through a small plug of Celite, dried over Na_2SO_4 and concentrated. The residue is purified using a SiO_2 column (ISCO), affording 4-[5-Methyl-4-(1-methyl-1H-pyrazol-4-yl)-2-nitro-phenoxy]-piperidine-1-carboxylic acid tert-butyl ester. MS (ES+): 417.3 (MH+), 439.2 (MNa+).

Steps 3, 4 and 5

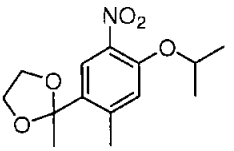
[0098] Utilizing the same procedures described in the synthesis of **Example 1** (Steps 7, 8 and 9) and final purification using preparative RP LC-MS affords 5-Methyl-N^2-[4-methyl-5-(1-methyl-1H-pyrazol-4-yl)-2-(piperidin-4-yloxy)-phenyl]-N^4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (**35**). MS (ES+): 576.3 (MH+).

Example 4

1-(5-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-4-isopropoxy-2-methyl-phenyl)-ethanone (**36**)

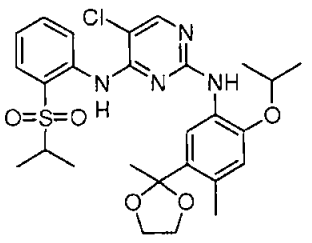


Step 1: 2-(4-Isopropoxy-2-methyl-5-nitro-phenyl)-2-methyl-[1,3]dioxolane



[0100] A mixture of 1-(4-Isopropoxy-2-methyl-5-nitro-phenyl)-ethanone (0.788 g, 3.32 mmol), ethyleneglycol (1.8 mL), and *p*-toluenesulfonic acid monohydrate (6.3 mg) in 60 mL of benzene is heated at reflux with a Dean-Stark trap for 18 hrs. The reaction mixture is diluted with 100 mL of ethyl acetate and successively washed with 100 mL each of aqueous saturated $NaHCO_3$, H_2O, and saturated brine. The organic phase is dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo, affording 2-(4-Isopropoxy-2-methyl-5-nitro-phenyl)-2-methyl-[1,3]dioxolane as yellow crystals. MS (ES+): 282.2 (MH+).

Steps 2 and 3: 5-Chloro-N2-[2-isopropoxy-4-methyl-5-(2-methyl-[1,3]dioxolan-2-yl)-phenyl]-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine



[0101] Utilizing the same procedures described in the synthesis of **Example 1** (Steps 7 and 8), using 2-(4-Isopropoxy-2-methyl-5-nitro-phenyl)-2-methyl-[1,3]dioxolane from the previous

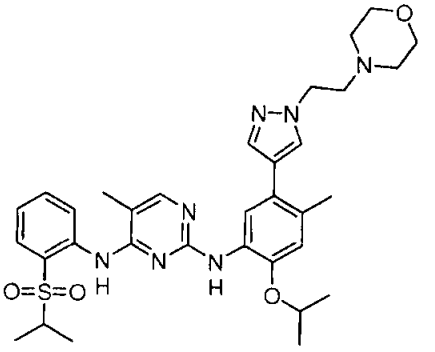
step as starting material and purification using silica gel chromatography (gradient 2% to 20% EtOAc in hexanes) affords 5-Chloro-N2-[2-isopropoxy-4-methyl-5-(2-methyl-[1,3]dioxolan-2-yl)-phenyl]-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine as a white solid. MS (ES+): 561.2 (MH+).

Step 4

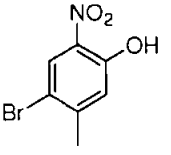
[0102] A solution of 5-Chloro-N2-[2-isopropoxy-4-methyl-5-(2-methyl-[1,3]dioxolan-2-yl)-phenyl]-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine from the previous step (84 mg, 0.15 mmol) in 5 mL 1,4-dioxane is treated with 1 mL of aqueous 1N HCl at 22 °C for 2 hrs. The reaction is worked up and affords 1-(5-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-4-isopropoxy-2-methyl-phenyl)-ethanone (**36**). MS (ES+): 517.2 (MH+).

Example 5

N^2-{2-Isopropoxy-4-methyl-5-[1-(2-morpholin-4-yl-ethyl)-1H-pyrazol-4-yl]-phenyl}-5-methyl-N^4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (**37**)



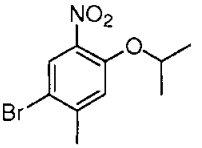
Step 1: 4-Bromo-5-methyl-2-nitro-phenol



[0103] 4-Bromo-3-methyl-phenol (1.122 g, 6.00 mmol) and $Yb(CF_3SO_3)_3$ (372 mg) in 30 mL dichloromethane is treated with 0.38 mL of conc. HNO_3 at 22 °C. After stirring at the same temperature for 1 hr, an additional 0.1 mL of conc. HNO_3 is added, and the reaction is stirred for an additional hour. The reaction mixture is washed with H_2O, dried over anhydrous magnesium

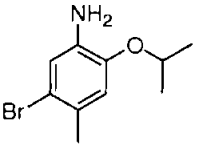
sulfate, filtered and concentrated. The residue is purified using a SiO_2 column (ISCO), affording a mixture of 4-Bromo-5-methyl-2-nitro-phenol as yellow crystals and its regioisomer by-product as orange crystals.

Step 2: 1-Bromo-4-isopropoxy-2-methyl-5-nitro-benzene



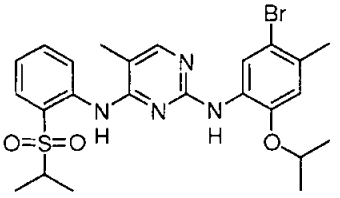
[0104] To a mixture of 4-Bromo-5-methyl-2-nitro-phenol from the previous step (0.66 g, 2.84 mmol), 2-propanol (0.262 mL), and triphenylphosphine (894 mg) in 10 mL THF is added diisopropyl asodicarboxylate (0.671 mL) at 22 °C. The reaction mixture is concentrated in vacuo. The residue is purified using a SiO_2 column (ISCO), affording 1-Bromo-4-isopropoxy-2-methyl-5-nitro-benzene as a bright yellow solid.

Step 3: 5-Bromo-2-isopropoxy-4-methyl-phenylamine



[0105] To 1-Bromo-4-isopropoxy-2-methyl-5-nitro-benzene from the previous step (0.734 g, 2.68 mmol) and iron (powder, 325 mesh, 1.05 g) in 20 mL ethanol is added 1 mL of 1N aqueous HCl with cooling in an ice bath. Following this addition, the reaction is heated at reflux for 2 hrs. Then an additional 0.5 g of iron is added and the reaction is heated at reflux for an additional 2 hrs. The reaction mixture is cooled down and filtered though a pad of Celite. The filtrate is concentrated in vacuo, affording 5-Bromo-2-isopropoxy-4-methyl-phenylamine as an orange oil. The product is used for the next step without further purification.

Step 4: N2-(5-Bromo-2-isopropoxy-4-methyl-phenyl)-5-methyl-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine



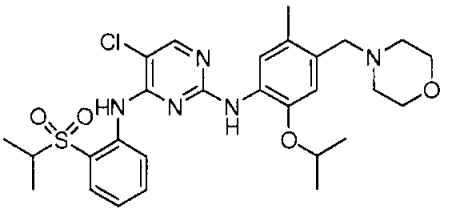
[0106] 5-Bromo-2-isopropoxy-4-methyl-phenylamine from the previous step (537 mg, 2.20 mmol) and 2-chloro-*N*-(2-(*iso*-propylsulfonyl)phenyl)-5-methylpyrimidin-4-amine (**Intermediate 1**, 652 mg, 2.00 mmol) in the presence of methanesulfonic acid (0.143 mL) in 4 mL 2-propanol are condensed at 140 °C for 30 min in a sealed tube under microwave irradiation. Following workup, N2-(5-Bromo-2-isopropoxy-4-methyl-phenyl)-5-methyl-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine is obtained. MS (ES+): 535.1 (MH+).

Step 5

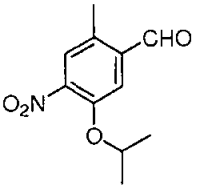
[0107] A mixture of N2-(5-Bromo-2-isopropoxy-4-methyl-phenyl)-5-methyl-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine from the previous step (53 mg, 0.099 mmol), 4-{2-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-ethyl}-morpholine (Boron Molecular, 61 mg 0.20 mmol), K_3PO_4 (58 mg), $Pd_2(dba)_3$ (10 mg), and tricyclohexylphosphine (8 mg) in 1 mL of 1,4-dioxane/H2O (3/1 v/v) is heated in a sealed tube at 150 °C for 20 min under microwave radiation. The reaction mixture is filtered through a small plug of Celite and concentrated. Final purification using preparative RP LC-MS affords N2-{2-Isopropoxy-4-methyl-5-[1-(2-morpholin-4-yl-ethyl)-1H-pyrazol-4-yl]-phenyl}-5-methyl-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (**37**). MS (ES+): 634.3 (MH+).

Example 6

5-Chloro-N2-(2-isopropoxy-5-methyl-4-morpholin-4-ylmethyl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (**60**)

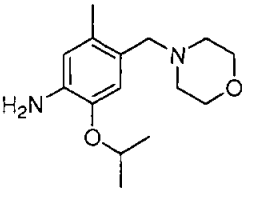


Steps 1 and 2: 1-Chloro-5-isopropoxy-2-methyl-4-nitro-benzene



[0108] To a mixture of 1-chloro-2-methyl-4-nitro-5-isopropoxy-benzene (**Intermediate 4**, 870 mg, 3.77mmol), vinylboronic acid dibutyl ester (1.24 mL, 5.6 mmol), and sodium carbonate (2.8 g, 26.4mmol) in THF/H_2O (20/5 mL) is added dichlorobis(triphenylphospine) palladium (II) (132 mg, 5% mmol). The reaction tube is sealed, the mixture is purged with N_2 for 3 min and then heated at 90°C under N_2 for overnight. The reaction is cooled to room temperature and poured into saturated aqueous ammonia chloride solution. The crude reaction mixture is extracted with ethyl acetate (3 x 100 mL). The organic extracts are combined, washed with brine and concentrated. The crude product is purified with silica gel column chromatography (10% ethyl acetate in hexanes) to afford 1-methyl-5-nitro-4-propoxy-2-vinyl-benzene as a yellow solid. 1-Methyl-5-nitro-4-propoxy-2-vinyl-benzene obtained from the previous step (360 mg, 1.63mmol) is dissolved in DCM (20 mL) and is cooled to -78 °C. O_3 (g) is bubbled into the solution until the solution's color turns blue/gray. The solution is then purged with N_2 (g) until the blue color disappears. The solution is warmed to room temperature and treated with triphenylphospine resin (2 g) pre-swelled in DCM (30 mL). After 30 min, the mixture is filtered, and the filtrate is concentrated to afford 2-methyl-4-nitro-5-propoxy-benzaldehyde as yellow solid.

Steps 3 and 4: 2-Isopropoxy-5-methyl-4-morpholin-4-ylmethyl-phenylamine



[0109] To a solution of 2-methyl-4-nitro-5-propoxy-benzaldehyde obtained in the previous step (34 mg, 0.152 mmol) in MeOH/THF (0.5/0.5 mL), is added acetic acid (5 drops). The mixture is stirred at room temperature for 1 hour. Sodium cyanoborohydride (20 mg, 0.30 mmol) is then added. After stirring for 30 min, the reaction is quenched by adding saturated

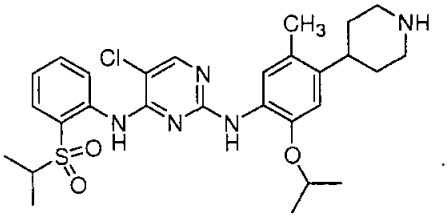
aqueous ammonium chloride solution. The reaction mixture is extracted with ethyl acetate (3 x 5 mL). The organic phases are combined and concentrated to afford the amine product as an yellow oil which is directly used for the next step without further purification. To a solution of the product obtained in the previous step in methanol (5 mL), is added Pd/C (10% on carbon, 2 mg). The mixture is hydrogenated under 1 atm hydrogen. After 4 hours, the mixture is filtered and concentrated. The aniline product obtained (yellow solid), is used in the next step without further purification.

Step 5

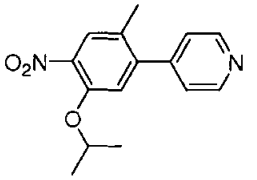
[0110] To a mixture of the aniline product obtained in the previous step (0.152 mmol), (2,5-dichloro-pyrimidin-4-yl)-[2-(propane-2-sulfonyl)-phenyl]-amine (**Intermediate 2**, 52 mg, 0.152 mmol), cesium carbonate (99 mg, 0.30 mmol) and xantphos (8 mg, 0.02mmol) in THF (2 mL), is added palladium acetate (2 mg, 5% mmol) in a microwave tube. The mixture is purged with N_2 for 3 min and then the sealed tube is heated at 150 °C for 20 min. under microwave irradiation. The reaction is filtered, concentrated, and purified by mass-trigger preparative RP LC-MS to afford the title compound 5-Chloro-N^2-(2-isopropoxy-5-methyl-4-morpholin-4-ylmethyl-phenyl)-N^4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (**60**) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35(s, 1H), 8.38 (d, 1H0, 7.93 (d, 1H), 7.59 (m, 2H), 7.41-7.36 (m, 2H), 4.70-4.63(br, 1H), 4.30-4.18 (br, 2H), 4.15-4.10 (br, 2H), 4.00-3.97 (br, 2H), 3.52-3.46 (br, 2H), 3.20 (m, 1H), 2.95-2.84 (br, 2H), 2.24 (s, 3H), 1.31 (d, 12H); ESMS *m/z* 574.2 ($M + H^+$).

Example 7

5-Chloro-N^2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N^4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (**66**)

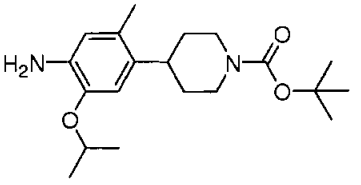


Step 1: 4-(5-Isopropoxy-2-methyl-4-nitro-phenyl)-pyridine



[0111] 4-Pyridineboronic acid (147 mg, 1.20 mmol, 1.1 equiv.) is dissolved in a 2:1 v/v mixture of dioxane and H_2O (15 mL) and N_2 is bubbled through for 5 minutes. Tris(dibenzylidene acetone)dipalladium (0) (100 mg, 0.109 mmol, 0.1 equiv.), 2-dicyclohexylphosphine-2'-6'-dimethoxy biphenyl (112 mg, 0.272 mmol, 0.25 equiv.), 1-chloro-5-isopropoxy-2-methyl-4-nitro-benzene (**Intermediate 4**, 250 mg, 1.09 mmol, 1.0 equiv.) and K_3PO_4 (462 mg, 2.18 mmol, 2.0 equiv.) are added under a N_2 blanket. The reaction vessel is sealed and heated with microwave irradiation to 150 °C for 20 min. After cooling to room temperature, the reaction is diluted with ethyl acetate and washed with 1 N aqueous NaOH (2x), the organic layer is then dried over Na_2SO_4 and filtered. After concentration, the crude product is purified by silica gel chromatography (gradient from hexanes to 30% ethyl acetate in hexanes) to give 4-(5-Isopropoxy-2-methyl-4-nitro-phenyl)-pyridine as a brown solid: ESMS *m/z* 273.1 ($M + H^+$).

Steps 2 and 3: 4-(4-Amino-5-isopropoxy-2-methyl-phenyl)-piperidine-1-carboxylic acid tert-butyl ester



[0112] 4-(5-Isopropoxy-2-methyl-4-nitro-phenyl)-pyridine from the previous step(438 mg, 1.61 mmol) dissolved in acetic acid (30 mL) is treated with TFA (0.24 mL, 3.22 mmol) and PtO_2 (176 mg, 40% w/w). The reaction mixture is vigorously stirred under 1 atm. H_2 for 36 hours. The reaction mixture is filtered and the filtrate is concentrated under vacuum. The resulting residue is diluted with ethyl acetate and washed with 1 N aqueous NaOH (2x), the organic layer is then dried over Na_2SO_4 and filtered. After concentration, the crude product (391 mg) is dissolved in anhydrous CH_2Cl_2 (30 mL). TEA is added (0.44 mL, 3.15, 2 equiv.) followed by Boc_2O (344 mg, 1.57 equiv, 1 equiv.). The reaction is stirred at room temperature for 30 min.

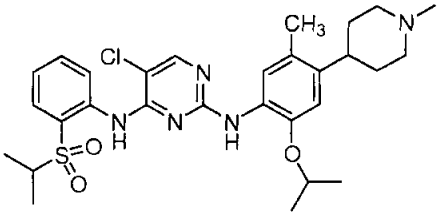
The reaction is concentrated under vacuum. The resulting residue is purified by silica gel chromatography (gradient from hexanes to 30% ethyl acetate in hexanes) to give 4-(4-amino-5-isopropoxy-2-methyl-phenyl)-piperidine-1-carboxylic acid tert-butyl ester as a sticky foam: ESMS *m/z* 293.1 $(M\text{-}t\text{Bu}+H)^+$.

Steps 4 and 5

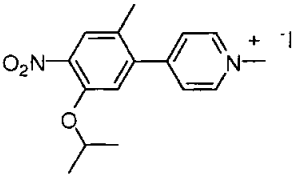
[0113] 4-(4-Amino-5-isopropoxy-2-methyl-phenyl)-piperidine-1-carboxylic acid tert-butyl ester (170 mg, 0.488 mmol) from the previous step, (2,5-Dichloro-pyrimidin-4-yl)-[2-(propane-2-sulfonyl)-phenyl]-amine (**Intermediate 2**, 169 mg, 0.488 mmol, 1 equiv.), xantphos (28 mg, 0.049 mmol, 0.1 equiv.), palladium acetate (5.5 mg, 0.024 mmol, 0.05 equiv.), and Cs_2CO_3 (477 mg, 1.46 mmol, 3 equiv.) are dissolved in anhydrous THF (6 mL). N_2 is bubbled through the reaction mixture for 5 minutes and then the reaction vessel is sealed and heated with microwave irradiation to 150 °C for 20 min. The reaction is filtered and the filtrate concentrated under vacuum. After concentration, the crude product is purified by silica gel chromatography (gradient from hexanes to 30% ethyl acetate in hexanes) to give 4-(4-{5-chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-methyl-phenyl)-piperidine-1-carboxylic acid tert-butyl ester as a yellow film: ESMS *m/z* 658.3 $(M + H^+)$. This product (105 mg, 0.160 mmol) is dissolved in CH_2Cl_2 (3 mL) and treated with TFA (3 mL). After 45 min., the reaction is concentrated under vacuum. 1 N HCl in Et_2O (5 mL x 2) is added causing the product HCl salt to precipitate. The solvent is removed by decantation. The resulting 5-Chloro-N^2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N^4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (**66**) is dried under high vacuum, generating an off-white powder: ^{1}H NMR (400 MHz, DMSO-d_6 + trace D_2O) δ 8.32 (s, 1H), 8.27 (d, 1H), 7.88 (d, 1H), 7.67 (dd, 1H), 7.45 (dd, 1H), 7.42 (s, 1H), 6.79 (s, 1H), 4.56-4.48 (m, 1H), 3.49-3.32 (m, 3H), 3.10-2.91 (m, 3H), 2.09 (s, 3H), 1.89-1.77 (m, 4H), 1.22 (d, 6H), 1.13 (d, 6H); ESMS *m/z* 558.1 $(M + H^+)$.

Example 8

5-Chloro-N^2-[2-isopropoxy-5-methyl-4-(1-methyl-piperidin-4-yl)-phenyl]-N^4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (**67**)

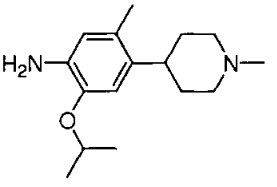


Step 1: 4-(5-Isopropoxy-2-methyl-4-nitro-phenyl)-1-methyl-pyridinium iodide



[0114] 4-(5-Isopropoxy-2-methyl-4-nitro-phenyl)-pyridine (**Example 7, Step 1,** 217 mg, 0.797 mmol) is dissolved in anhydrous THF (9 mL). Iodomethane (0.10 mL, 1.61 mmol, 2 equiv.) is added and the reaction is stirred at 40 °C in a sealed tube for 2 days. The volatiles are removed under vacuum generating 4-(5-Isopropoxy-2-methyl-4-nitro-phenyl)-1-methyl-pyridinium iodide as a brown solid: ESMS *m/z* 287.1 (M^+).

Steps 2 and 3: 2-Isopropoxy-5-methyl-4-(1-methyl-piperidin-4-yl)-phenylamine



[0115] 4-(5-Isopropoxy-2-methyl-4-nitro-phenyl)-1-methyl-pyridinium iodide from the previous step (0.697 mmol) is dissolved in CH_3OH (20 mL) and cooled to 0 °C. $NaBH_4$ (264 mg, 6.97 mmol, 10 equiv.) is slowly added. After this addition is complete, the cooling bath is removed and the reaction is stirred at room temperature for 1 h. The reaction is quenched by the slow addition of 1N aqueous HCl (14 mL). The CH_3OH is partially removed by vacuum. The resulting residue is partitioned between EtOAc and 1 N aqueous NaOH. Additional 50 % aqueous NaOH is added until the aqueous layer pH >12. The EtOAc layer is washed with 1 N aqueous NaOH (2x), the organic layer is then dried over Na_2SO_4, filtered, and concentrated under vacuum. After concentration, the crude product (175 mg) is dissolved in acetic acid (10 mL). TFA (0.15 mL, 3 equiv.) and PtO_2 (53 mg, 30% w/w) are added and the reaction is placed

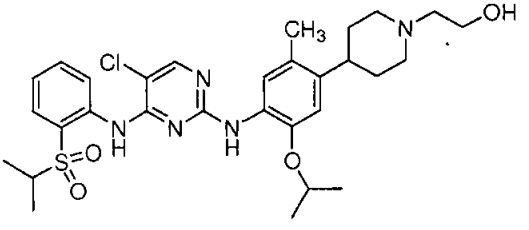
under 50 psi H_2 gas in a Parr Shaker for 14 h. The reaction mixture is filtered and the filtrate is concentrated under vacuum. The resulting residue is partitioned between EtOAc and 1 N aqueous NaOH. Additional 50% aqueous NaOH is added until the aqueous layer pH >12. The EtOAc layer is washed with 1 N aqueous NaOH (2x), the organic layer is then dried over Na_2SO_4, filtered, and concentrated under vacuum to give 2-Isopropoxy-5-methyl-4-(1-methyl-piperidin-4-yl)-phenylamine which is used in Step 4 without further purification: ESMS *m/z* 263.2 ($M + H^+$).

Step 4

[0116] Utilizing the same procedures described in the synthesis of **Example 7** (Step 4) and final purification using preparative RP LC-MS affords 5-Chloro-N^2-[2-isopropoxy-5-methyl-4-(1-methyl-piperidin-4-yl)-phenyl]-N^4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (**67**) as a pale yellow powder: (HCl salt, DMSO-d_6 + trace D_2O) δ 8.28 (s, 1H), 8.19 (d, 1H), 7.86 (d, 1H), 7.66 (dd, 1H), 7.45 (dd, 1H), 7.37 (s, 1H), 6.77 (s, 1H), 4.56-4.49 (m, 1H), 3.51-3.37 (m, 3H), 3.16-3.08 (m, 2H), 2.98-2.88 (m, 1H), 2.77 (s, 3H), 2.05 (s, 3H), 1.90-1.81 (m, 4H), 1.19 (d, 6H), 1.11 (d, 6H); ESMS *m/z* 572.2 ($M + H^+$).

Example 9

2-[4-(4-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-methyl-phenyl)-piperidin-1-yl]-ethanol (**72**)

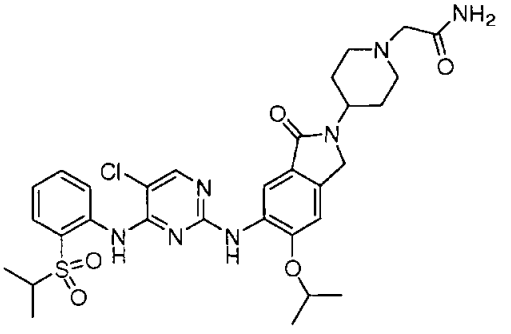


[0117] 5-Chloro-N^2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N^4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (**Example 7**, 0.087 mmol) is dissolved in anhydrous DMF (1 mL). TEA (0.04 mL, 0.262 mmol, 3 equiv.) is added followed by 2-bromo-ethanol (0.019 mL, 0.262 mmol, 3 equiv.) dissolved in anhydrous DMF (0.7 mL). The reaction vessel is sealed and heated at 70 °C for 12 h. After cooling to room temperature, the reaction is diluted with ethyl acetate and washed with 1 N aqueous NaOH (5x), the organic layer is then dried over Na_2SO_4 and filtered. After concentration, the crude product is purified using preparative RP

LC-MS to give 2-[4-(4-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-methyl-phenyl)-piperidin-1-yl]-ethanol (**72**) as a yellow powder: ESMS *m/z* 602.2 ($M + H^+$).

Example 10

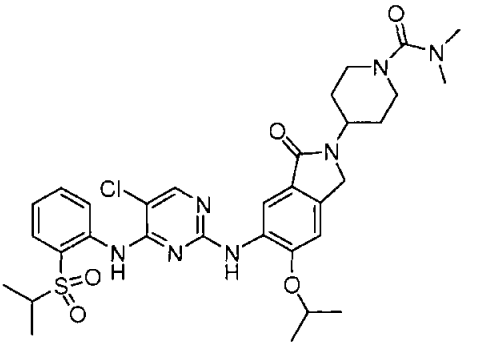
2-[4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidin-1-yl]-acetamide (**149**)



[0118] To a mixture of 6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-piperidin-4-yl-2,3-dihydro-isoindol-1-one (**Example 1**, 20 mg, 0.033 mmol) and triethylamine (23 uL, 0.165 mmol) in DMF (1.5 mL), is added 2-bromo-acetamide (10 mg, 0.066 mmol). The mixture is stirred at 60 °C for 4 hours. The reaction is filtered and the filtrate is purified by mass-trigger preparative RP LC-MS to afford the title compound 2-[4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidin-1-yl]-acetamide (**136**) as a white solid: ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.41 (d, 1H), 8.27 (s, 1H), 8.21 (br, 1H), 7.93 (dd, 1H), 7.73 (m, 1H), 7.40 (dd, 1H), 7.30 (s, 1H), 4.52 (s, 2H), 4.45-4.37 (m, 1H), 4.19-4.15 (br, 2H), 3.87-3.78 (br, 2H), 2.37-2.19 (m, 2H), 2.20-2.15 (m, 1H), 1.40 (d, 6H), 1.25 (d, 6H); ESMS *m/z* 656.2 ($M + H^+$).

Example 11

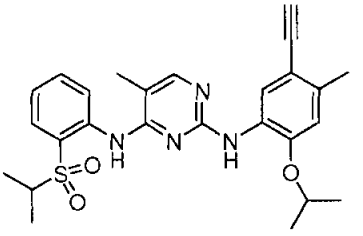
4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid dimethylamide (**155**)



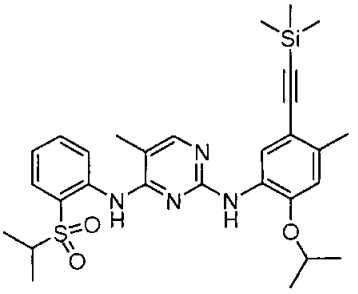
[0119] To a mixture of 6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-piperidin-4-yl-2,3-dihydro-isoindol-1-one (**Example 1**, 20 mg, 0.033 mmol) and triethylamine (23 uL, 0.165 mmol) in DMF (1.5 mL) is added dimethylcarbamyl chloride (11 mg, 0.1 mmol). The mixture is stirred at room temperature for 1 hour. The reaction is filtered and the filtrate is purified by mass-trigger preparative RP LC-MS to afford the title compound 4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid dimethylamide (**155**) as a white solid: ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.29 (s, 1H), 8.26 (br, 1H), 7.96 (dd, 1H), 7.93 (s, 1H), 7.72(dd, 1H), 7.48 (dd, 1H), 7.35 (s, 1H), 4.50 (s, 2H), 4.35-4.29 (m, 1H), 3.83 (d, 2H), 3.38-3.30 (m, 2H), 3.02-2.95 (m, 3H), 2.88 (s, 6H), 1.88-1.84 (m, 3H), 1.36 (d, 6H), 1.25 (d, 6H); ESMS *m/z* 670.2 ($M + H^+$).

Example 12

N2-(5-Ethynyl-2-isopropoxy-4-methyl-phenyl)-5-methyl-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (**257**)



Step 1: N2-(2-Isopropoxy-4-methyl-5-trimethylsilanylethynyl-phenyl)-5-methyl-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine



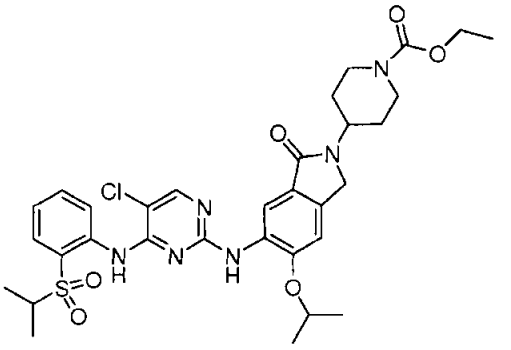
[0120] A mixture of N2-(5-Bromo-2-isopropoxy-4-methyl-phenyl)-5-methyl-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (**Example 5, Step 4**. 110 mg, 0.21 mmol), ethynyl-trimethyl-silane (0.14 mL), N,N-diisopropyl ethylamine (0.10 mL), $PdCl_2(PhCN)_2$ (12 mg), $^tBu_3PHBF_4$ (17 mg), and CuI (4 mg) in 1 mL 1,4-dioxane is stirred at 22 °C for 20 hrs followed by heating at 60 °C for an additional 2 hrs. The reaction mixture is filtered through a small Celite plug and concentrated. The residue is purified over a 4 g SiO_2 column (ISCO) using a gradient of 0 to 20% ethyl acetate in hexanes as eluent, affording N2-(2-Isopropoxy-4-methyl-5-trimethylsilanylethynyl-phenyl)-5-methyl-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine as a yellow viscous oil.

Step 2

[0121] A solution of N2-(2-Isopropoxy-4-methyl-5-trimethylsilanylethynyl-phenyl)-5-methyl-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine from the previous step (0.102 g, 0.18 mmol) in 2.5 mL THF is treated with TBAF (0.5 mL, 1M in THF) and 30 µL AcOH at 22 °C for 2 hrs. The reaction mixture is concentrated and the residue is purified using a 4 g SiO_2 column (ISCO), affording N2-(5-Ethynyl-2-isopropoxy-4-methyl-phenyl)-5-methyl-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (**257**). MS (ES+): 479.2 (MH+).

Example 13

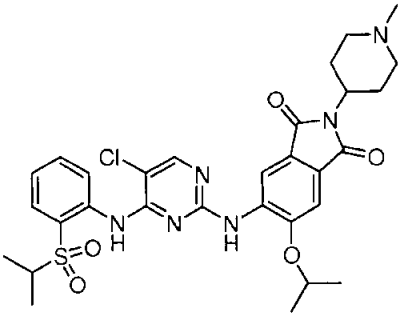
4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid ethyl ester (**175**)



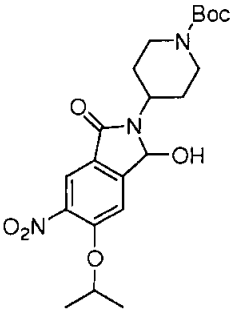
[0122] To a mixture of 6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-piperidin-4-yl-2,3-dihydro-isoindol-1-one (**Example 1,** 15 mg, 0.025 mmol) and triethylamine (37.5 uL, 0.25 mmol) in DMF (0.5 mL), is added ethyl chloroformate (5.4 mg. 0.05 mmol). The mixture is stirred at room temperature for 1 hour. The crude reaction mixture is purified by mass-trigger preparative RP LC-MS to afford the title compound 4-(6-{5-chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid ethyl ester (**175**) as a white solid. ^{1}H NMR 400 MHz (DMSO-d_6 with trace D_2O) δ 8.55 (d, 1H), 8.32 (s, 1H), 8.14 (s, 1H), 7.82 (dd,1H), 7.74 (t, 1H), 7.34 (t, 1H), 7.28 (s, 1H), 4.73 (m, 2H), 4.39 (s, 2H), 4.12 (m, 2H), 4.06 (q, 2H), 3.46 (m, 1H), 2.92 (m 2H), 1.76 (m, 2H), 1.68 (m, 2H), 1.29 (d, 6H), 1.20 (t, 3H), 1.17 (d, 6H); MS m/z 671 (M+1).

Example 14

5-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-6-isopropoxy-2-(1-methyl-piperidin-4-yl)-isoindole-1,3-dione (**176**)

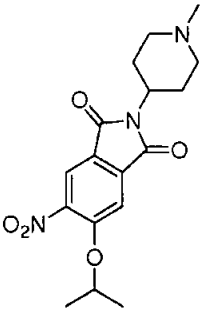


Step 1: 4-(1-Hydroxy-6-isopropoxy-5-nitro-3-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester



[0123] 4-(4-Isopropoxy-5-nitro-2-vinyl-benzoylamino)-piperidine-1-carboxylic acid tert-butyl ester (**Example 1, Step 3,** 1.2 g, 2.77 mmol) dissolved in 50 mL of DCM is cooled to -78 °C. Ozone gas is bubbled through this solution until the starting material is consumed and then nitrogen gas is bubbled through the solution for 5 min. The reaction mixture is warmed to room temperature. Triphenylphosphine-resin (2.77 g) in 10 mL of DCM is added and the resulting mixture is stirred for 1.5 h. The resin is removed by filtration and the filtrate is concentrated. Silica gel chromatography (5% MeOH in DCM) affords 4-(1-hydroxy-6-isopropoxy-5-nitro-3-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester; MS m/z 336.2 (M-Boc + H^+).

Steps 2, 3 and 4: 5-Isopropoxy-2-(1-methyl-piperidin-4-yl)-6-nitro-indan-1,3-dione



[0124] To the solution of 4-(1-hydroxy-6-isopropoxy-5-nitro-3-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester from the previous step (173.9 mg, 0.4 mmol) in DMF (4 mL) is added pyridinum dichromate (286.5 mg, 0.8 mmol) in one portion. After stirring at room temperature for 2 h, the reaction mixture is poured into 25 mL of water and the product is extracted with EtOAc. The organic extracts are dried over Na_2SO_4, filtered and

concentrated *in vacuo* to give crude 4-(5-isopropoxy-6-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester, which is directly used in the next step without further purification.

[0125] To a solution of 4-(5-isopropoxy-6-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester generated in the previous step in 3 mL of DCM is added TFA (3 mL). The reaction mixture is stirred at room temperature for 1 h. After concentration, water (5 mL) is added to the crude reaction mixture, the resulting mixture is neutralized to pH=8 by adding $NaHCO_3$, and the product is extracted with DCM. The organic extracts are dried over Na_2SO_4, filtered and concentrated *in vacuo* to give crude 5-isopropoxy-6-nitro-2-piperidin-4-yl-isoindole-1,3-dione, which is directly used in the next step without further purification.

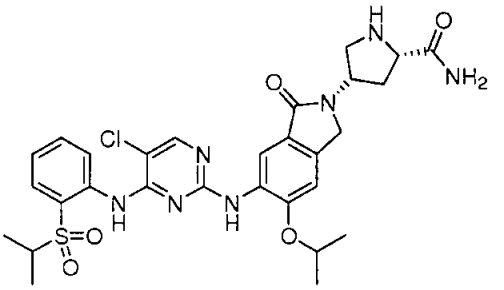
[0126] To a solution of the 5-isopropoxy-6-nitro-2-piperidin-4-yl-isoindole-1,3-dione generated in the previous step in THF (5 mL) and methanol (5 mL) are added formaldehyde (30 uL, 0.4 mmol) and 2 drops of AcOH sequentially. The reaction mixture is stirred at room temperature for 1h, then sodium cyanoborohydride (50.4 mg, 0.8 mmol) is added in one portion and the resulting mixture is stirred for an additional 30 min. The reaction is quenched by the addition of saturated aqueous NH_4Cl followed by concentration *in vacuo* to give an oily residue. This oil is partitioned between EtOAc and brine. The organic extract is dried over Na_2SO_4, filtered and concentrated. Silica gel chromatography (5% MeOH in DCM) affords 5-isopropoxy-2-(1-methyl-piperidin-4-yl)-6-nitro-indan-1,3-dione; MS m/z 347.2 (M+1).

Steps 5 and 6

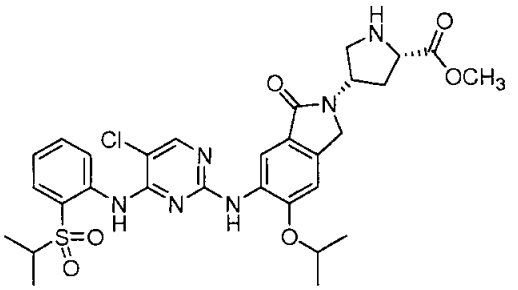
[0127] Following the procedures previously described **(Example 1, Steps 7 and 8)** using the product from Step 4 generates the title compound 5-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-6-isopropoxy-2-(1-methyl-piperidin-4-yl)-isoindole-1,3-dione (**176**) as a yellow solid. ^{1}H NMR 400 MHz (DMSO-d_6 with trace D_2O) δ 8.44 (s, 2H), 8.39 (s, 1H), 7.87 (dd, 1H), 7.78 (dt, 1H), 7.45 (s, 1H), 7.41 (m, 1H), 4.91(m, 2H), 4.25(m, 2H), 3.51 (m, 3H), 3.10(m, 2H), 2.77(s, 3H), 1.80(m, 2H), 1.35(d, 6H), 1.13(d, 6H); MS m/z 627 (M+1).

Example 15

(2S, 4S)-4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro-isoindol-2-yl)-pyrrolidine-2-carboxylic acid amide (**177**)



Step 1: *(2S, 4S)*-4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro-isoindol-2-yl)-pyrrolidine-2-carboxylic acid methyl ester



[0128] Following the procedures previously described (**Example 1**) using *N*-Boc-*cis*-4-amino-L-proline methyl ester in place of 4-amino-piperidine-1-carboxylic acid tert-butyl ester, generates *(2S, 4S)*-4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro-isoindol-2-yl)-pyrrolidine-2-carboxylic acid methyl ester: MS m/z 643.2 (M+1).

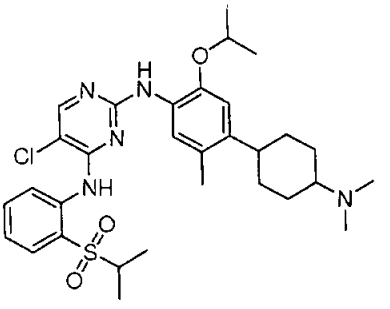
Step 2

[0129] *(2S, 4S)*-4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro-isoindol-2-yl)-pyrrolidine-2-carboxylic acid methyl ester generated in Step 1 (20 mg, 0.03 mmol) is dissolved in 7 N ammonia solution in MeOH (3 mL, 21 mmol). The resulting solution is heated using microwave irradiation to 120 °C for 1 h. After cooling to room temperature, the reaction mixture is concentrated *in vacuo*, neutralized to pH=8 with saturated aqueous $NaHCO_3$, and extracted with DCM. The organic extracts are dried

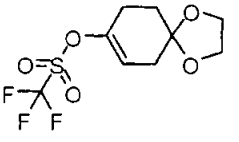
over Na_2SO_4, filtered, and concentrated *in vacuo* to give *(2S, 4S)*-4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro-isoindol-2-yl)-pyrrolidine-2-carboxylic acid amide (**177**) as a yellow solid. ^{1}H NMR 400 MHz (DMSO-d_6 with trace D_2O) δ 8.47(d, 1H), 8.25 (s, 1H), 8.07 (s, 1H), 7.78 (dd, 1H), 7.68 (m, 1H), 7.31(t, 1H), 7,24 (s, 1H), 4,71 (m, 2H), 4.43 (dd, 2H), 3.60 (m, 1H), 3.44 (m, 1H), 3.35 (m,1H), 2.63 (m, 1H), 2.28 (m, 1H), 1.22 (d, 6H), 1.10 (d, 6H); MS m/z 628 (M+1).

Example 16

5-Chloro-N2-[4-(4-dimethylamino-cyclohexyl)-2-isopropoxy-5-methyl-phenyl]-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (**21**)



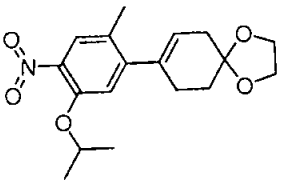
Step 1: 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate



[0130] A solution of 0.5 M KHMDS in toluene (4.7 mL, 2.34 mmol) is added to a solution of 1,4-dioxaspiro[4.5]decan-8-one (1.80 mmol) and N-phenyltrifluoromethanesulfonimide (2.34 mmol) in dry THF (18 mL) at -78°C under argon. After stirring at -78°C for 4 hours, the mixture is quenched with H_2O, extracted with diethyl ether and dried with $MgSO_4$. After workup and silica flash chromatography (hexane/EtOAc 90:10), 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate is isolated: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.66 (m, 1H), 3.98 (m, 4H), 2.53 (m, 2H), 2.40 (m, 2H), 1.90 (t, 2H). MS (ES+): 289.0 $(M+1)^+$.

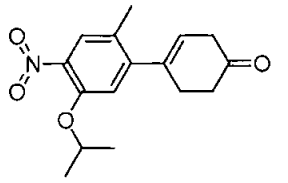
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Step 2: 8-(5-isopropoxy-2-methyl-4-nitrophenyl)-1,4-dioxaspiro[4.5]dec-7-ene



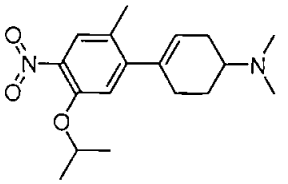
[0131] A stirred solution of the 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (0.03 mmol) and 2-(5-isopropoxy-2-methyl-4-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**Intermediate 5**, 0.04 mmol) in THF (3 mL), containing $[Pd(PPh_3)_4]$ (0.013 mmol) and $K_3PO_4 \cdot H_2O$ (0.045 mmol), is heated to 80°C under argon for 16 hours. After workup and silica flash chromatography (hexane/EtOAc 4:1), 8-(5-isopropoxy-2-methyl-4-nitrophenyl)-1,4-dioxaspiro[4.5]dec-7-ene is obtained. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (s, 1H), 6.82 (s, 1H), 5.74 (m, 1H), 4.65 (m, 1H), 4.04 (m, 4H), 2.47 (m, 4H), 2.27 (s, 3H), 1.89 (t, 2H), 1.29 (d, 6H). MS (ES+): 334.16 $(M+1)^+$.

Step 3: 4-(5-isopropoxy-2-methyl-4-nitrophenyl)cyclohex-3-enone



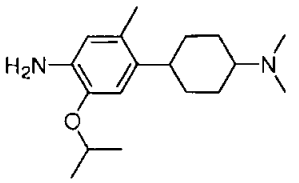
[0132] A solution of 8-(5-isopropoxy-2-methyl-4-nitrophenyl)-1,4-dioxaspiro[4.5]dec-7-ene (0.1 mmol) in 2.5 mL of TFA and CH_2Cl_2 (1:4 v/v), is stirred at room temperature for 6 hours. After workup and silica flash chromatography (hexane/EtOAc 4:1), 4-(5-isopropoxy-2-methyl-4-nitrophenyl)cyclohex-3-enone is obtained. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (s, 1H), 6.81 (s, 1H), 5.73 (m, 1H), 4.62 (m, 1H), 3.07 (m, 2H), 2.68 (m, 4H), 2.27 (s, 3H), 1.37 (d, 6H). MS (ES+): 290.13 $(M+1)^+$.

Step 4: 4-(5-isopropoxy-2-methyl-4-nitrophenyl)-N,N-dimethylcyclohex-3-enamine



[0133] To a solution of 4-(5-isopropoxy-2-methyl-4-nitrophenyl)cyclohex-3-enone (0.1 mmol) and dimethylamine (0.11 mmol) in 2 mL of 1,2-dicholoroethane, is added AcOH (0.1 mmol) and $NaBH(OAc)_3$ (0.11 mmol). The reaction mixture is stirred at room temperature for 10 hours. After workup and silica flash chromatography (CH_2Cl_2/MeOH 9:1), 4-(5-isopropoxy-2-methyl-4-nitrophenyl)-N,N-dimethylcyclohex-3-enamine is obtained. MS (ES+): 319.19 $(M+1)^+$.

Step 5: 4-(4-(dimethylamino)cyclohexyl)-2-isopropoxy-5-methylaniline



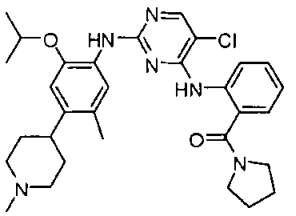
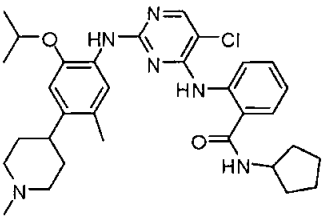
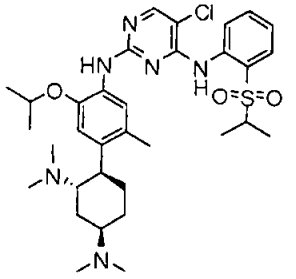
[0134] To a solution of 4-(5-isopropoxy-2-methyl-4-nitrophenyl)-N,N-dimethylcyclohex-3-enamine (0.1 mmol) in 10 mL of MeOH, is added Pd/C (5 mg) under argon. The suspension is stirred under 1 atm. H_2 for 6 hours. After filtering, solvent is removed and 4-(4-(dimethylamino)cyclohexyl)-2-isopropoxy-5-methylaniline is obtained. MS (ES+): 291.24 $(M+1)^+$.

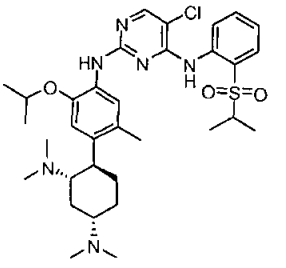
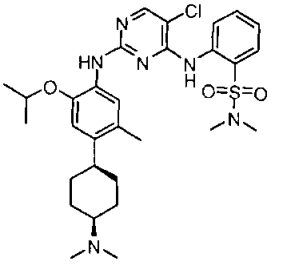
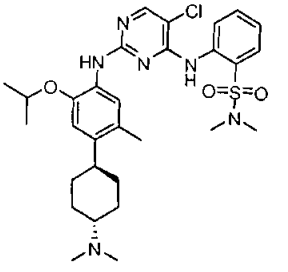
Step 6

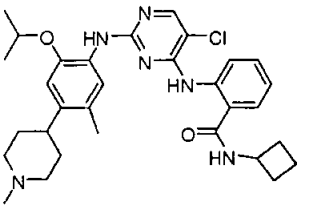
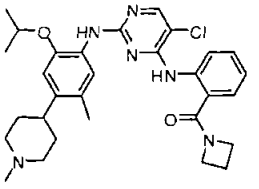
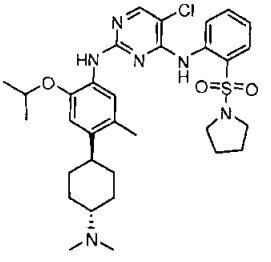
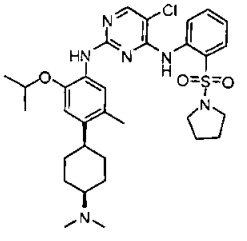
[0135] Following the procedure previously described **(Example 7, Step 4)** using the product from Step 5 generates the title compound 5-Chloro-N2-[4-(4-dimethylamino-cyclohexyl)-2-isopropoxy-5-methyl-phenyl]-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (**21**). ^1H NMR (CD_3OD, 400 MHz) δ 8.36-8.38 (d, 1H), 8.20 (s, 1H), 7.97-7.99 (m, 1H), 7.69-7.73 (m, 1H), 7.46--7.52 (m, 2H), 6.89-7.02 (d, 1H), 4.60-4.66 (m, 1H), 3.37-3.39 (m, 1H), 3.00 (s, 3H), 2.90 (s, 3H), 2.17-2.22 (m, 4H), 1.64-2.01 (m, 8H), 1.25-1.32 (m, 12H); MS (ES+): 600.3 $(M+1)^+$.

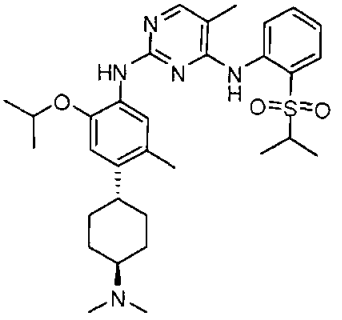
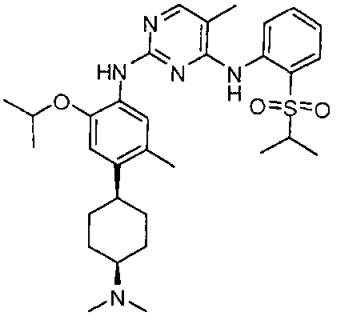
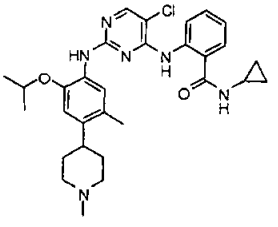
[0136] Exemplary compounds of the invention are set forth below. Table 1 shows exemplary compounds of Formula (1A).

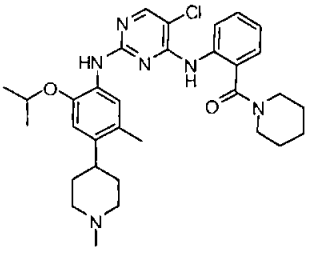
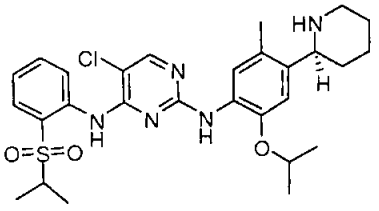
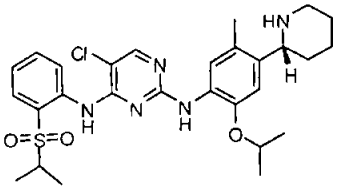
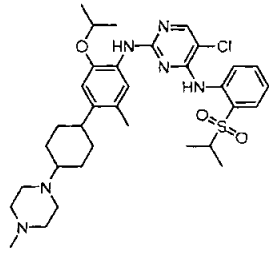
Table 1

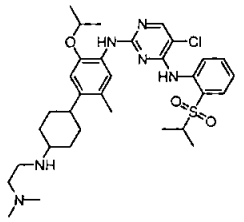
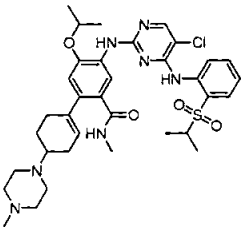
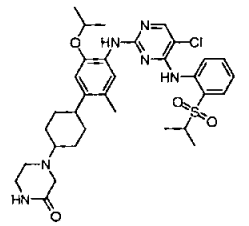
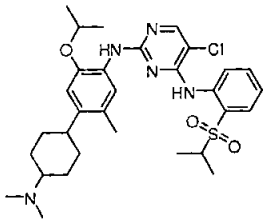
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
1	 (2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)phenyl)(pyrrolidin-1-yl)methanone	MS (ES^+): 563.1 $(M+1)^+$.
2	 2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)-N-cyclopentylbenzamide	MS (ES^+): 577.2 $(M+1)^+$.
3	 N2-(4-((1R,2S,4R)-2,4-bis(dimethylamino) cyclohexyl)-2-isopropoxy-5-methylphenyl)-5-chloro-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2.4-diamine	MS (ES^+): 643.3 $(M+1)^+$.

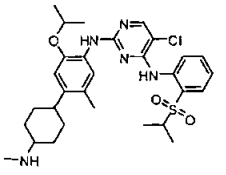
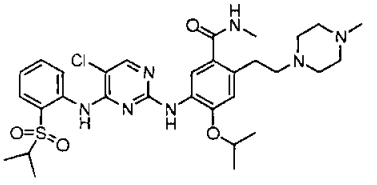
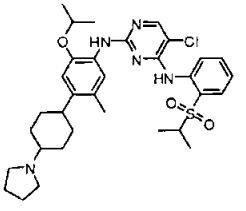
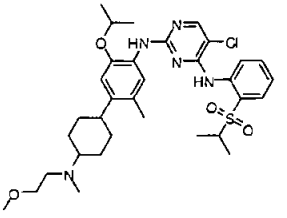
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
4	 N2-(4-((1R,2S,4S)-2,4-bis(dimethylamino) cyclohexyl)-2-isopropoxy-5-methylphenyl)-5-chloro-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 643.3 $(M+1)^+$.
5	 2-(5-chloro-2-(4-((1s,4s)-4-(dimethylamino) cyclohexyl)-2-isopropoxy-5-methylphenylamino) pyrimidin-4-ylamino)-N,Ndimethylbenzenesulfonamide	MS (ES^+): 601.2 $(M+1)^+$.
6	 2-(5-chloro-2-(4-((1r,4r)-4-(dimethylamino)cyclohexyl)-2-isopropoxy-5-methylphenylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide	MS (ES^+): 601.2 $(M+1)^+$.

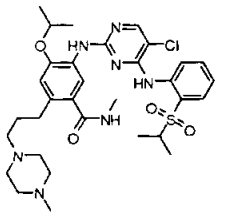
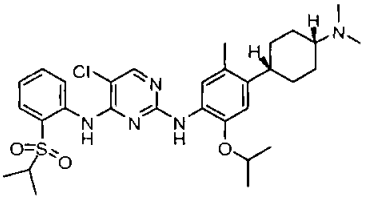
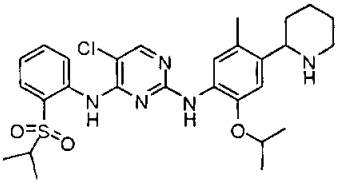
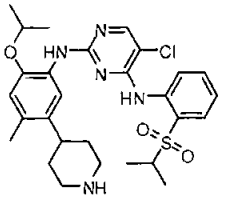
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
7	 2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)-N-cyclobutylbenzamide	MS (ES^+): 563.1 $(M+1)^+$.
8	 azetidin-1-yl(2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)phenyl)methanone	MS (ES^+): 549.1 $(M+1)^+$.
9	 5-chloro-N2-(4-((1r,4r)-4-(dimethylamino) cyclohexyl)-2-isopropoxy-5-methylphenyl)-N4-(2-(pyrrolidin-1-ylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 627.2 $(M+1)^+$.
10	 5-chloro-N2-(4-((1s,4s)-4-(dimethylamino) cyclohexyl)-2-isopropoxy-5-methylphenyl)-N4-(2-(pyrrolidin-1-ylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 627.2 $(M+1)^+$.

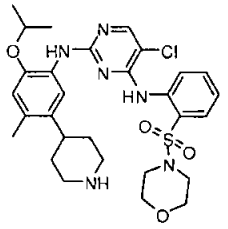
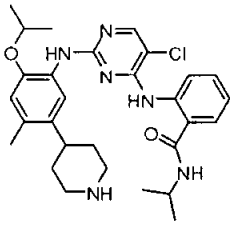
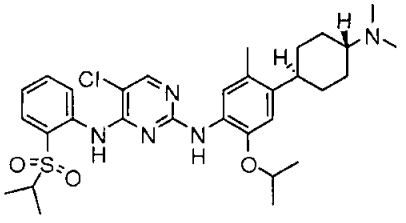
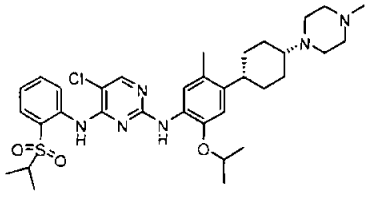
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
11	 N2-(4-((1r,4r)-4-(dimethylamino)cyclohexyl)-2-isopropoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl) phenyl)-5-methylpyrimidine-2,4-diamine	MS (ES^+): 580.8 $(M+1)^+$.
12	 N2-(4-((1s,4s)-4-(dimethylamino)cyclohexyl)-2-isopropoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl) phenyl)-5-methylpyrimidine-2,4-diamine	MS (ES^+): 580.8 $(M+1)^+$.
13	 2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)-N-cyclopropylbenzamide	MS (ES^+): 549.1 $(M+1)^+$.

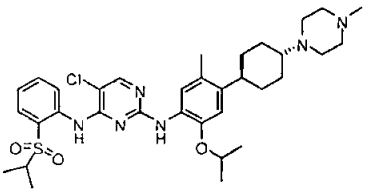
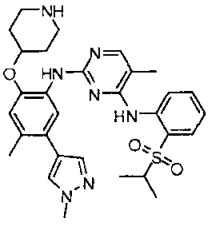
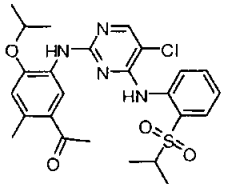
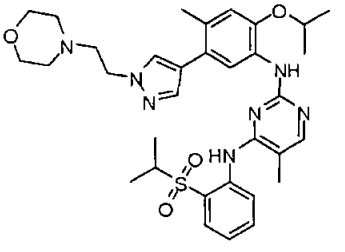
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
14	 (2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)phenyl)(piperidin-1-yl)methanone	MS (ES^+): 577.1 $(M+1)^+$.
15	 (S)-5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-2-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2.4-diamine	MS (ES^+): 558.1 $(M+1)^+$.
16	 (R)-5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-2-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl) pyrimidine-2,4-diamine	MS (ES^+): 558.1 $(M+1)^+$.
17	 (*cis,trans*) 5-Chloro-N2-{2-isopropoxy-5-methyl-4-[4-(4-methyl-piperazin-1-yl)-cyclohexyl]-phenyl}-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine	^{1}H NMR (CD_3OD, 400 MHz) δ 8.34-8.37 (m, 1H), 8.17 (s, 1H), 7.89-7.96 (m, 1H), 7.64-7.71 (m, 1H), 7.42-7.49 (m, 2H), 6.86-6.96 (d, 1H), 4.55-4.65 (m, 1H), 3.34-3.53 (m, 1H), 2.15-2.91 (m, 12H), 1.94-1.97 (m, 4H), 1.23-1.72 (m, 20H); MS (ES^+): 654.8 $(M+1)^+$.

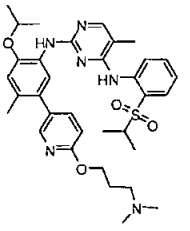
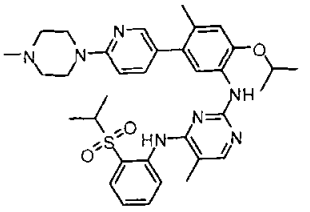
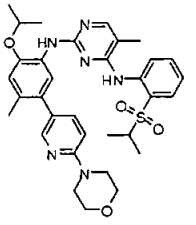
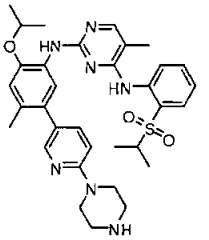
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
18	 (*cis,trans*) 5-chloro-N2-{4-[4-(2-dimethylamino-ethyl amino)-cyclohexyl]-2-isopropoxy-5-methyl-phenyl}-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine	^{1}H NMR (CD_3OD, 400 MHz) δ 8.35-8.37 (d, 1H), 8.20 (s, 1H), 7.97-8.00 (m, 1H), 7.7--7.74 (m, 1H), 7.46-7.51 (m, 2H), 6.89-7.03 (d, 1H), 4.60-4.64 (m, 1H), 3.30-3.60 (m, 5H), 3.01 (s, 6H), 2.81-2.84 (m, 1H), 1.25-2.30 (m, 24H); MS (ES^+): 643.3 $(M+1)^+$.
19	 5-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-4-isopropoxy-N-methyl-2-[4-(4-methyl-piperazin-1-yl)-cyclohex-1-enyl]-benzamide	^{1}H NMR (CD_3OD, 400 MHz) δ 8.51-8.56 (t, 1H), 8.41 (s, 1H), 8.19 (s, 1H), 7.86-7.89 (m, 1H), 7.54--7.58 (m, 1H), 7.27-7.31 (m, 1H), 6.97-7.00 (m, 1H), 4.77-4.84 (m, 1H), 2.66-3.32 (m, 15H), 1.22-2.21 (m, 18H); MS (ES^+): 696.2 $(M+1)^+$.
20	 4-[4-(4-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-methyl-phenyl)-cyclohexyl]-piperazin-2-one	^{1}H NMR (CD_3OD, 400 MHz) δ 8.34-8.36 (d, 1H), 8.21 (s, 1H), 7.98-8.00 (m, 1H), 7.69-7.73 (m, 1H), 7.45--7.52 (m, 2H), 6.90-7.01 (d, 1H), 4.60-4.66 (m, 1H), 3.99 (s, 2H), 3.36-3.62 (m, 6H), 1.65-2.42 (m, 12H), 1.24-1.31 (m, 12H); MS (ES^+): 655.3 $(M+1)^+$.
21	 5-Chloro-N2-[4-(4-dimethylamino-cyclohexyl)-2-isopropoxy-5-methyl-phenyl]-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine	^{1}H NMR (CD_3OD, 400 MHz) δ 8.36-8.38 (d, 1H), 8.20 (s, 1H), 7.97-7.99 (m, 1H), 7.69-7.73 (m, 1H), 7.46--7.52 (m, 2H), 6.89-7.02 (d, 1H), 4.60-4.66 (m, 1H), 3.37-3.39 (m, 1H), 3.00 (s, 3H), 2.90 (s, 3H), 2.17-2.22 (m, 4H), 1.64-2.01 (m, 8H), 1.25-1.32 (m, 12H); MS (ES^+): 600.3 $(M+1)^+$.

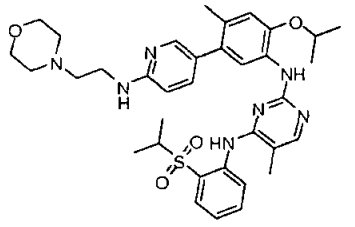
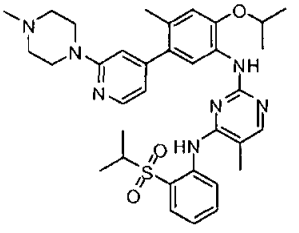
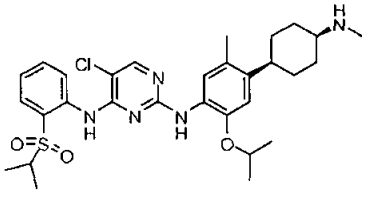
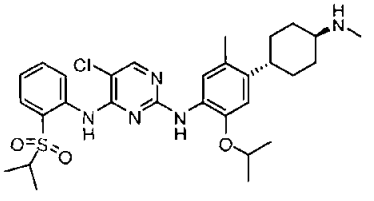
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
22	 5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-methylamino-cyclohexyl)-phenyl]-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine	^{1}H NMR (CD_3OD, 400 MHz) δ 8.32-8.34 (d, 1H), 8.22 (s, 1H), 7.98-8.00 (m, 1H), 7.69-7.73 (m, 1H), 7.49--7.53 (m, 1H), 7.40-7.41 (d, 1H), 6.91-7.02 (d, 1H), 4.61-4.66 (m, 1H), 3.36-3.40 (m, 1H), 2.74-2.78 (d, 3H), 2.17-2.28 (m, 4H), 1.64-2.03 (m, 8H), 1.24-1.31 (m, 12H); MS (ES^+): 586.2 $(M+1)^+$.
23	 5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-(2-(4-methylpiperazin-1-yl)ethyl)benzamide	MS (ES^+): 645.2 $(M+1)^+$
24	 5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-pyrrolidin-1-yl-cyclohexyl)-phenyl]-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine	^{1}H NMR (CD_3OD, 400 MHz) δ 8.36-8.38 (d, 1H), 8.20 (s, 1H), 7.97-7.99 (m, 1H), 7.69-7.73 (m, 1H), 7.45--7.52 (m, 2H), 6.88-7.02 (d, 1H), 4.60-4.66 (m, 1H), 3.65-3.85 (m, 2H), 3.32-3.34 (m, 1H), 3.16-3.20 (m, 2H), 2.77-2.96 (m, 1H), 1.22-2.35 (m, 28H); MS (ES^+): 626.3 $(M+1)^+$.
25	 5-Chloro-N2-(2-isopropoxy-4-{4-[(2-methoxy-ethyl)-methyl-amino]-cyclohexyl}-5-methyl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine	^{1}H NMR (CD_3OD, 400 MHz) δ 8.36-8.38 (d, 1H), 8.20-8.21 (m, 1H), 7.96-7.99 (m, 1H), 7.69-7.73 (m, 1H), 7.45--7.54 (m, 2H), 6.90-7.02 (d, 1H), 4.60-4.66 (m, 1H), 3.32-3.77 (m, 8H), 2.90-2.99 (m, 3H), 2.77-2.96 (m, 1H), 1.22-2.33 (m, 24H); MS (ES^+): 644.3 $(M+1)^+$.

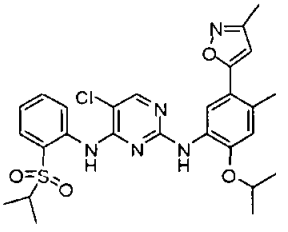
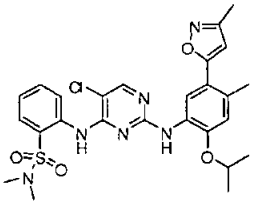
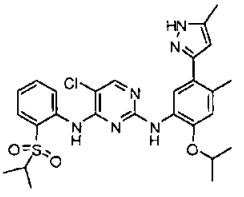
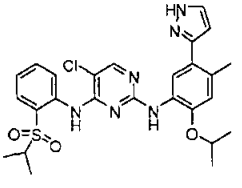
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
26	 5-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-4-isopropoxy-N-methyl-2-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide	^{1}H NMR (CD_3OD, 400 MHz) δ 8.44-8.46 (d, 1H), 8.25 (s, 1H), 8.13 (s, 1H), 7.94-7.96 (m, 1H), 7.64-7.67 (m, 1H), 7.42--7.46 (m, 1H), 7.06 (s, 1H), 4.77-4.83 (m, 1H), 3.48-3.54 (m, 8H), 3.32-3.35 (m, 1H), 3.06-3.10 (m, 2H), 2.96 (s, 3H), 2.81-2.87 (m, 5H), 2.16-2.20 (m, 2H), 1.27-1.39 (m, 12H); MS (ES^+): 658.3 $(M+1)^+$.
27	 5-chloro-N2-(4-((1s,4s)-4-(dimethylamino) cyclohexyl)-2-isopropoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 600.2 $(M+1)^+$.
28	 5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-2-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 558.2 $(M+1)^+$.
29	 5-chloro-N2-(2-isopropoxy-4-methyl-5-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl) pyrimidine-2,4-diamine	MS (ES^+): 558.2 $(M+1)^+$.

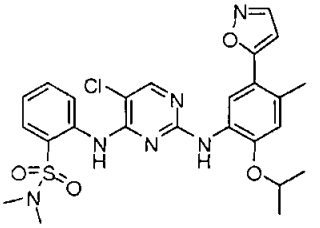
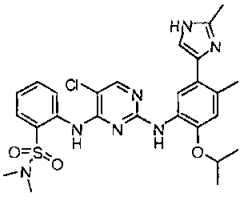
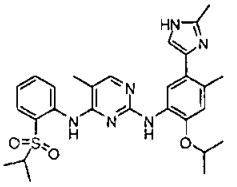
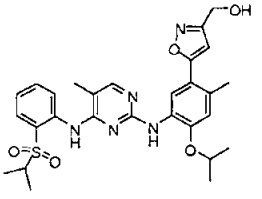
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
30	 5-chloro-N2-(2-isopropoxy-4-methyl-5-(piperidin-4-yl)phenyl)-N4-(2(morpholinosulfonamido) phenyl)pyrimidine-2,4-diamine	MS (ES^+): 601.2 $(M+1)^+$.
31	 2-(2-(2-isopropoxy-4-methyl-5-(piperidin-4-yl)phenylamino)-5-chloropyrimidin-4-ylamino)-N-isopropylbenzamide	MS (ES^+): 537.3 $(M+1)^+$.
32	 5-chloro-N2-(4-((1r,4r)-4-(dimethylamino) cyclohexyl)-2-isopropoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 600.3 $(M+1)^+$.
33	 5-chloro-N2-(2-isopropoxy-5-methyl-4-((1s,4s)-4-(4-methylpiperazin-1-yl)cyclohexyl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 655.3 $(M+1)^+$.

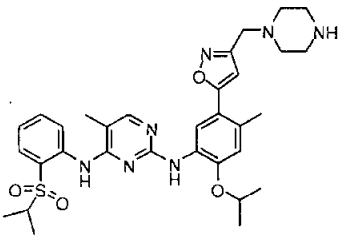
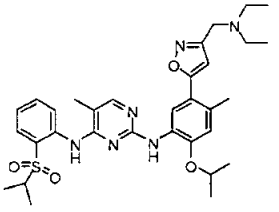
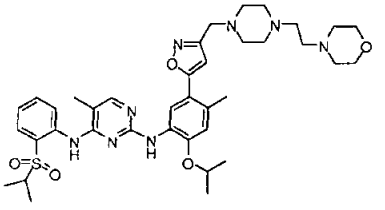
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
34	 5-chloro-N2-(2-isopropoxy-5-methyl-4-((1r,4r)-4-(4-methylpiperazin-1-yl)cyclohexyl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 655.3 $(M+1)^+$.
35	 5-Methyl-N2-[4-methyl-5-(1-methyl-1H-pyrazol-4-yl)-2-(piperidin-4-yloxy)-phenyl]-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine	1.10 (6H, d, J=5.7), 1.89 (2H, br), 2.03 (2H, br), 2.16 (3H, s), 2.32 (3H, s), 3.05 (2H, br), 3.49 (3H, br), 3.89 (3H, s), 4.72 (1H, br), 7.06 (1H, s), 7.21 (1H, br), 7.30 (1H, br), 7.41 (1H, br.s), 7.46 (1H, br.s), 7.69 (1H, s), 7.79 (1H, d, J= 7.4), 7.95 (1H, br), 8.04 (1H, br.s), 9.79 (2H, br.s). MS (ES^+): 576.3 $(M+1)^+$.
36	 1-(5-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-4-isopropoxy-2-methyl-phenyl)-ethanone	1.10 (6H, d, J=5.7), 1.89 (2H, br), 2.03 (2H, br), 2.16 (3H, s), 2.32 (3H, s), 3.05 (2H, br), 3.49 (3H, br), 3.89 (3H, s), 4.72 (1H, br), 7.06 (1H, s), 7.21 (1H, br), 7.30 (1H, br), 7.41 (1H, br.s), 7.46 (1H, br.s), 7.69 (1H, s), 7.79 (1H, d, J= 7.4), 7.95 (1H, br), 8.04 (1H, br.s), 9.79 (2H, br.s). MS (ES^+): 517.2 $(M+1)^+$.
37	 N2-{2-Isopropoxy-4-methyl-5-[1-(2-morpholin-4-yl-ethyl)-1H-pyrazol-4-yl]-phenyl}-5-methyl-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine	1.14 (6H, d, J=6.8), 1.25 (6H, d, J=6.0), 2.12 (3H, s), 2.33 (3H, s), 2.52 (overlapping with DMSO), 3.14 (2H, very br.) 3.45 (1H, sept, J=6.8), 3.70 (4H, very br), 3.93 (2H, very br), 4.6 (1 or 2H, br.S), 4.63 (1H, sept, J= 6.1), 6.99 (1H, s), 7.23 (2H, m), 7.53 (1H, s), 7.78 (2H, m)7.91 (1H, s), 8.01 (1H, s), 8.33 (1H, br.s), missing anilino NH. MS (ES^+): 634.3 $(M+1)^+$.

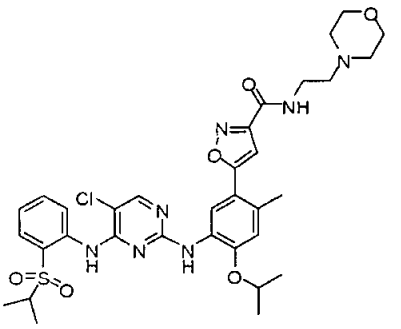
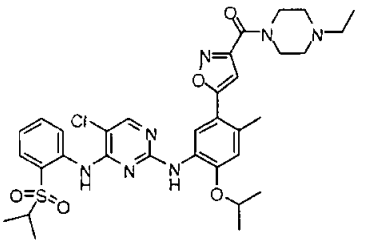
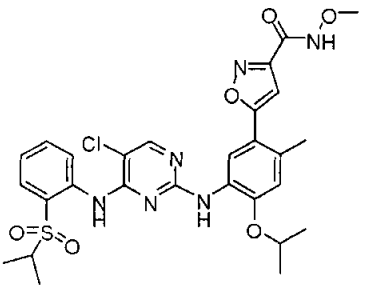
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
38	 N2-(5-(6-(3-(dimethylamino)propoxy)pyridin-3-yl)-2-isopropoxy-4-methylphenyl)-N4-(2-(isopropyl sulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine	1.06 (6H, d, J=6.7), 1.28 (6H, d, J=6.0), 2.15 (6H, s), 2.19 (2H, br.m), 2.80 (3H, s), 2.82 (3H, s), 3.25 (2H, m), 3.39 (1H, m), 4.39 (2H, t, J=6.1), 4.70 (1H, sept, J=6.1), 6.86 (1H, d, J=8.5), 7.07 (1H, s), 7.19 (1H, br.s), 7.35 (2H, br.s), 7.48 (1H, br.m)7.74 (1H, br.d, J=6.4), 7.84 (2H, br.s), 8.05 (1H, br.s), 9.76 (1H, s), 10.15 (1H, br.s). MS (ES^+): 633.8 $(M+1)^+$.
39	 N2-(2-isopropoxy-4-methyl-5-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)-5-methylpyrimidine-2,4-diamine	1.06 (6H, d, J=6.7), 1.28 (6H, d, J=6.0). 2.15 (6H, s), 2.19 (2H, br.m), 2.80 (3H, s), 2.82 (3H, s). 3.25 (2H, m), 3.39 (1H, m), 4.39 (2H, t, J=6.1), 4.70 (1H, sept, J=6.1), 6.86 (1H, d, J=8.5), 7.07 (1H, s), 7.19 (1H, br.s), 7.35 (2H, br.s), 7.48 (1H, br.m)7.74 (1H, br.d, J=6.4), 7.84 (2H, br.s), 8.05 (1H, br.s), 9.76 (1H, s), 10.15 (1H, br.s). MS (ES^+): 630.8 $(M+1)^+$.
40	 N2-(2-isopropoxy-4-methyl-5-(6-morpholinopyridin-3-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine	1.08 (6H, d, J=6.7), 1.28 (6H, d, J=6.0), 2.15 (3H, s), 2.19 (3H, s), 3.59 (4H, br), 3.78 (4H, br), 4.70 (1H, sept, J=6.1), 7.02 (1H, br.s), 7.07 (1H. s),7.24 (1H, br.s), 7.35 (2H, br.s), 7.49 (1H, br.s), 7.75 (1H, br.d, J=6.8), 7.81 (1H, br.s), 7.86 (1H, br), 8.04 (1H, br.s), 9.76 (1H, br.s). MS (ES^+): 617.8 $(M+1)^+$.
41	 N2-(2-isopropoxy-4-methyl-5-(6-(piperazin-1-yl)pyridin-3-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)-5-methylpyrimidine-2,4-diamine	1.12 (6H, d, J=6.7), 1.31 (6H, d, J=6.0), 2.09 (3H, s), 2.18 (3H,s), 3.25 (4H, br.s), 3.39 (1H, sept, J=6.8), 3.75 (4H, br.t, J=5.1), 4.68 (1H, sept, J=6.1), 6.90 (1H, d, J=9.0), 6.98 (1H, s), 7.01 (1H, br.s), 7.11 (1H, br.s), 7.44 (1H, s), 7.47 (1H,s) 7.70 (1H, d, J=7.7), 7.92 (1H, s) 8.04 (1H, s), 8.23 (1H, br.s), 8.90 (1H, br.s), 8.94 (1H, br.s). MS (ES^+): 616.8 $(M+1)^+$.

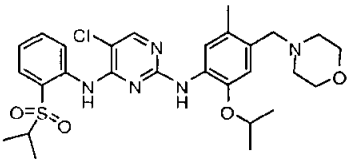
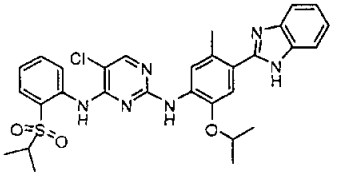
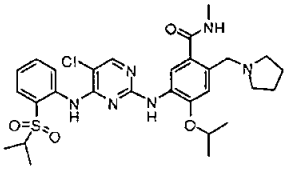
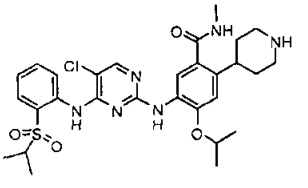
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
42	 N2-(5-(6-(2-morpholinoethylamino)pyridin-3-yl)-2-isopropoxy-4-methylphenyl)-N4-(2-(isopropyl-sulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine	MS (ES^+): 660.8 $(M+1)^+$.
43	 N2-(2-isopropoxy-4-methyl-5-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)-5-methylpyrimidine-2,4-diamine	1.13 (6H, d, J=6.8), 1.32 (6H, d, 6.0), 20.9 (3H, s), 2.20 (3H, s), 2.76 (3H, br.s), 3.1 (4H, very br.), 3.38 (H_2O overlap), 3.40 (1H, sept, J=6.8), 4.36 (1H, very br), 4.70 (1H, sept, J=6.0), 6.60 (1H, d, J=4.7), 6.73 (1H, s), 7.00 (3h, br) 7.68 (1H, s), 7.72 (1H, dd, J=1.8, 7.5), 7.95 (1H, s), 8.03 (1H, s), 8.12 (1H, d, J=5.1), 8.31 (1H, br.d, J=7.6), 8.91 (1H, s). 630.8 $(M+1)^+$.
44	 5-chloro-N2-(2-isopropoxy-5-methyl-4-((1s,4s)-4-(methylamino)cyclohexyl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 586.3 $(M+1)^+$
45	 5-chloro-N2-(2-isopropoxy-5-methyl-4-((1r,4r)-4-(methylamino)cyclohexyl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2.4-diamine	MS (ES^+): 586.3 $(M+1)^+$

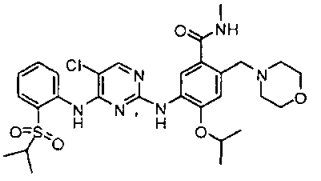
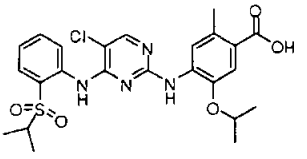
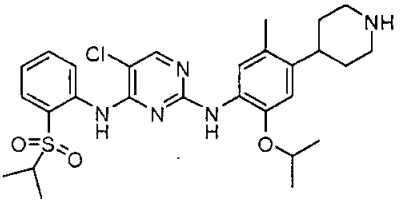
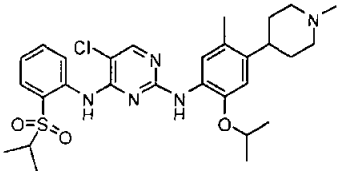
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
46	 5-chloro-N2-(2-isopropoxy-4-methyl-5-(3-methylisoxazol-5-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	1H NMR (400 MHz, MeOD-d4) δ 8.15 (1H, s), 8.12 (1H, d, *J* = 7.6 Hz), 7.93 (1H, s), 7.78 (1H, d, *J* = 7.6 Hz), 7.20 (2H, m), 6.96 (1H, s), 6.18 (1H, s), 4.68 (1H, m), 3.28 (1H, m), 2.38 (3H, s), 2.23 (3H, s), 1.26 (6H, d, *J* = 6.0Hz), 1.16 (6H, d, *J* = 6.8 Hz) .MS (ES^+): 556.2 $(M+1)^+$.
47	 2-(5-chloro-2-(2-isopropoxy-4-methyl-5-(3-methylisoxazol-5-yl)phenylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide	1H NMR (400 MHz, MeOD-d4) δ 8.20 (1H, s), 8.12 (1H, d, *J* = 7.6 Hz), 7.97 (1H, s), 7.78 (1H, d, *J* = 7.6 Hz), 7.20 (2H, m), 7.01 (1H, s), 6.24 (1H, s), 4.74 (1H, m), 2.68 (6H, s), 2.43 (3H, s), 2.29 (3H,s), 1.32 (6H, d, *J* = 6.0 Hz).MS (ES^+): 557.2 $(M+1)^+$.
48	 5-chloro-N2-(2-isopropoxy-4-methyl-5-(5-methyl-1H-pyrazol-3-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine	1H NMR (400 MHz, MeOD-d4) δ 8.29 (1H, s), 8.13 (1H, bs), 7.97 (1H, s), 7.87 (1H, d, *J* = 7.6 Hz), 7.75 (1H, s), 7.35 (2H, m), 7.09 (1H,s), 6.41 (1H, s), 4.80 (1H, m), 3.40 (1H, m), 2.50 (3H, s), 2.40 (3H, s), 1.36 (6H, d, *J* = 6.0 Hz), 1.25 (3H, d, *J* = 6.8 Hz). MS (ES^+): 555.2 $(M+1)^+$.
49	 5-chloro-N2-(2-isopropoxy-4-methyl-5-(1H-pyrazol-3-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine	1H NMR (400 MHz, MeOD-d4) δ 8.27 (1H, s), 8.20 (1H, bs), 7.90 (1H, d, *J* = 6.4 Hz), 7.81 (1H, bs), 7.67 (1H, s), 7.37 (2H, bs), 7.08 (1H.s), 6.45 (1H, s), 4.76 (1H, m), 3.38 (1H, m), 2.41 (3H, s), 1.35 (6H, d, *J* = 6.0 Hz), 1.25 (3H, d, *J* = 6.8 Hz).MS (ES^+): 541.2 $(M+1)^+$.

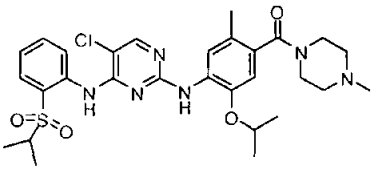
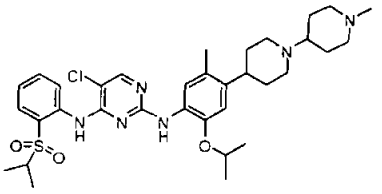
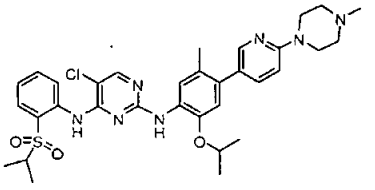
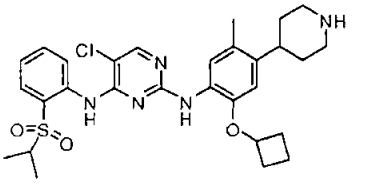
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
50	 2-(5-chloro-2-(2-isopropoxy-5-(isoxazol-5-yl)-4-methylphenylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide	1H NMR (400 MHz, MeOD-d4) δ 8.31 (1H, s), 8.16 (1H, s), 8.03 (1H, bs), 7.92 (1H, s), 7.74 (1H, d, *J* = 7.2 Hz), 7.17 (2H, bs), 6.99 (1H,s), 6.34 (1H, s), 4.69 (1H, m), 2.64 (6H, s), 2.39 (3H, s), 1.27 (6H, d, *J* = 6.0 Hz). MS (ES$^+$): 543.2 (M+1)$^+$.
51	 2-(5-chloro-2-(2-isopropoxy-4-methyl-5-(2-methyl-1H-imidazol-4-yl)phenylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide	1H NMR (400 MHz, MeOD-d4) δ 8.18 (1H, s), 7.94 (1H, d, *J* = 5.2 Hz), 7.72 (1H, s), 7.70 (1H, s), 7.29 (2H, bs), 7.21 (2H, bs), 7.00 (1H,s), 4.68 (1H, m), 2.65 (6H, s), 2.58 (3H, s), 2.28 (3H, s), 1.27 (6H, d, *J* = 6.0 Hz). .MS (ES$^+$): 556.2 (M+1)$^+$.
52	 5-chloro-N2-(2-isopropoxy-4-methyl-5-(2-methyl-1H-imidazol-4-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine	1H NMR (400 MHz, MeOD-d4) δ 8.10 (1H, bs), 7.90 (1H, s), 7.85 (1H, d, *J* = 7.6 Hz), 7.65 (1H, s), 7.48 (1H, bs), 7.36 (2H, bs), 7.12 (1H,s), 4.70 (1H, m), 3.39 (1H, m), 2.70 (3H, s), 2.40 (3H, s), 2.26 (3H, s), 1.34 (6H, d, *J* = 6.0 Hz), 1.24 (6H, d, *J* = 6.8 Hz). MS (ES$^+$): 535.2 (M+1)$^+$.
53	 (5-(5-(4-(2-(isopropylsulfonyl)phenylamino)-5-methylpyrimidin-2-ylamino)-4-isopropoxy-2-methylphenyl)isoxazol-3-yl)methanol	1H NMR (400 MHz, MeOD-d4) δ 8.39 (1H, s), 8.31 (1H, d, *J* = 8.0 Hz), 7.98 (1H, s), 7.81 (1H, d, *J* = 7.2 Hz), 7.19 (1H, bs), 7.10 (1H, bs), 6.97 (1H, s), 6.29 (1H,s), 4.78 (1H, m), 4.66 (2H, s), 3.39 (1H, m), 2.44 (3H, s), 2.18 (3H, s), 2.26 (3H, s), 1.41 (6H, d, *J* = 5.6 Hz), 1.27 (6H, d, *J* = 6.8 Hz). MS (ES$^+$): 552.6 (M+1)$^+$.

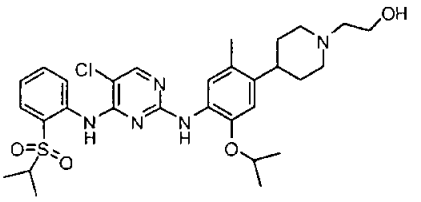
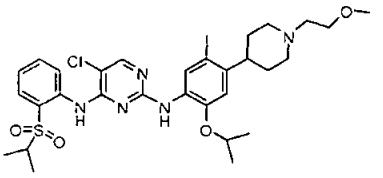
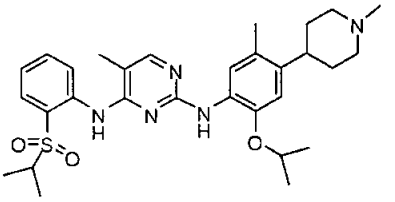
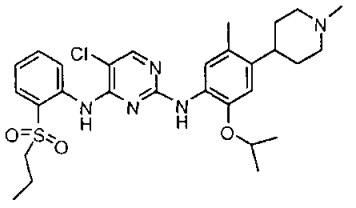
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
54	 N2-(2-isopropoxy-4-methyl-5-(3-((piperazin-1-yl)methyl)isoxazol-5-yl)phenyl)-N4-(2-(isopropyl-sulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine	1H NMR (400 MHz, MeOD-d4) δ 8.31 (1H, d, *J* = 8.4 Hz), 8.29 (1H, s), 7.88 (1H, s), 7.71 (1H, d, *J* = 8.0 Hz), 7.11 (1H, t, *J* = 8.8 Hz), 6.98 (1H, t, *J* = 7.2 Hz), 6.88 (1H, s), 6.25 (1H,s), 4.67 (1H, m), 3.59 (2H, s), 3.22 (1H, m), 3.03 (4H, bs), 2.61 (4H, bs), 2.35 (3H, s), 2.07 (3H, s), 1.30 (6H, d, *J* = 5.6 Hz), 1.17 (6H, d, *J* = 6.8 Hz). MS (ES$^+$): 620.8 (M+1)$^+$.
55	 N2-(5-(3-((diethylamino)methyl)isoxazol-5-yl)-2-isopropoxy-4-methylphenyl)-N4-(2-(isopropyl-sulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine	1H NMR (400 MHz, MeOD-d4) δ 8.35 (1H, s), 8.33 (1H, d, *J* = 8.4 Hz), 7.89 (1H, s), 7.72 (1H, d, *J* = 8.0 Hz), 7.15 (1H, t, *J* = 8.8 Hz), 7.01 (1H, t, *J* = 7.2 Hz), 6.90 (1H, s), 6.47 (1H,s), 4.69 (1H, m), 4.19 (2H, s), 3.24 (1H, m), 3.00 (4H, bs), 2.38 (3H, s), 2.08 (3H, s), 1.22 (6H, t, *J* = 7.2 Hz), 1.17 (6H, d, *J* = 6.8 Hz). MS (ES$^+$): 607.8 (M+1)$^+$.
56	 N2-(2-isopropoxy-4-methyl-5-(3-((4-(2-morpholinoethyl)piperazin-1-yl)methyl)isoxazol-5-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine	1H NMR (400 MHz, MeOD-d4) δ 8.31 (1H, d, *J* = 8.4 Hz), 8.28 (1H, s), 7.87 (1H, s), 7.70 (1H, d, *J* = 8.0 Hz), 7.08 (1H, t, *J* = 8.8 Hz), 6.99 (1H, t, *J* = 7.2 Hz), 6.87 (1H, s), 6.25 (1H,s), 4.66 (1H, m), 3.61 (4H, m), 3.55 (2H, s), 3.21 (1H, m), 2.34-2.59 (12H, m), 2.35 (3H, s), 2.06 (3H, s), 1.29 (6H, d, *J* = 6.0 Hz), 1.16 (6H, d, *J* = 6.8 Hz). MS (ES$^+$): 733.4 (M+1)$^+$.

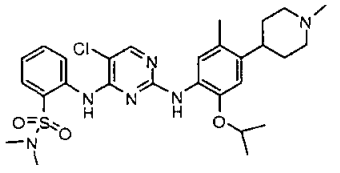
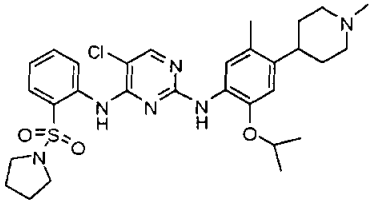
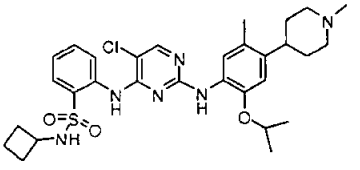
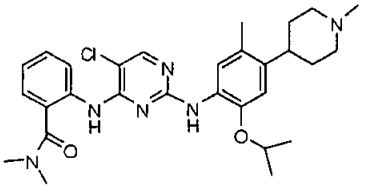
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
57	 5-(5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-2-methylphenyl)-N-(2-morpholinoethyl)isoxazole-3-carboxamide	1H NMR (400 MHz, MeOD-d4) δ 8.33 (1H, s), 8.17 (1H, bs), 7.93 (1H, s), 7.92 (1H, d, *J* = 7.2 Hz), 7.91 (1H, s), 7.37-7.39 (2H, m), 7.17 (1H, s), 6.83 (1H, s), 4.84 (1H, m), 4.11 (2H, dd, *J* = 2.8 and 12.8 Hz) 3.83-3.88 (4H, m), 3.70 (2H, d, *J* = 12.4 Hz), 3.42-3.48 (3H, m), 3.21 (2H, m), 2.54 (3H, s), 1.36 (6H, d, *J* = 6.0 Hz), 1.26 (6H, d, *J* = 6.8 Hz). MS (ES^+): 698.2 $(M+1)^+$.
58	 (5-(5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-2-methylphenyl)isoxazol-3-yl)(4-ethylpiperazin-1-yl)methanone	1H NMR (400 MHz, MeOD-d4) δ 8.33 (1H, s), 8.12 (1H, bs), 7.93 (1H, s), 7.95 (1H, s), 7.91 (1H, d, *J* = 8.8 Hz), 7.35-7.44 (2H, m), 7.15 (1H, s), 6.76 (1H, s), 4.85 (1H, m), 3.66-3.76 (4H, m) 3.38-3.43 (2H, m), 3.10 (2H, m), 2.54 (3H, s), 1.42 (3H, t, *J* = 7.2 Hz), 1.37 (6H, d, *J* = 6.0 Hz), 1.27 (6H, d, *J* = 6.8 Hz). MS (ES^+): 682.3 $(M+1)^+$.
59	 5-(5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-2-methylphenyl)-N-methoxyisoxazole-3-carboxamide	1H NMR (400 MHz, MeOD-d4) δ 8.17 (1H, s), 8.06 (1H, d, *J* = 8.0 Hz), 8.02 (1H, s), 7.77 (1H, d, *J* = 7.6 Hz), 7.21 (1H, bs), 7.12 (1H, t, *J* = 7.6 Hz), 6.97 (1H, s), 6.51 (1H, s). 4.71 (1H, m), 3.77 (3H, s), 3.29 (1H. m), 2.39 (3H, s), 1.28 (6H, d, *J* = 6.0 Hz), 1.17 (6H, d, *J* = 6.8 Hz). MS (ES^+): 615.1 $(M+1)^+$.

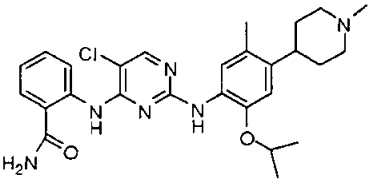
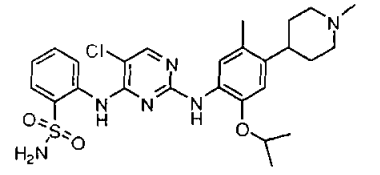
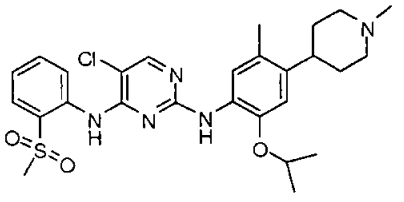
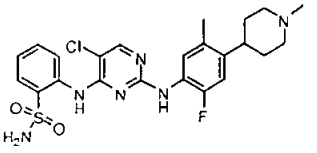
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
60	 5-Chloro-N2-(2-isopropoxy-5-methyl-4-morpholin-4-ylmethyl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine	1H NMR (400 MHz, CDCl3) 10.35(s, 1H), 8.38 (d, 1H0, 7.93 (d, 1H), 7.59 (m, 2H), 7.41-7.36 (m, 2H), 4.70-4.63(br, 1H), 4.30-4.18 (br, 2H), 4.15-4.10 (br, 2H), 4.00-3.97 (br, 2H), 3.52-3.46 (br, 2H), 3.20 (m, 1H), 2.95-2.84 (br, 2H), 2.24 (s, 3H), 1.31 (d, 12H). MS (ES^+): 574.2 $(M+1)^+$.
61	 N2-(4-(1H-benzo[d]imidazol-2-yl)-2-isopropoxy-5-methylphenyl)-5-chloro-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	1H NMR (400 MHz, CDCl3) 10.43 (s, 1H), 9.68 (s, 1H), 8.32 (d, 1H), 8.04 (s, 1H), 7.93 (d, 1H), 7.71-7.65 (m, 3H), 7.59 (s, 1H), 7.40-7.37 (, 3H), 4.46-4.43 (m, 1H), 3.31-3.20 (m, 1H), 2.38 (s, 3H), 1.32 (d, 6H), 1.15 (d, 6H). MS (ES^+): 591.2 $(M+1)^+$.
62	 5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-((pyrrolidin-1-yl)methyl)benzamide	MS (ES^+): 601.2 $(M+1)^+$.
63	 5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-(piperidin-4-yl)benzamide	1H NMR: (DMSO-d6 + trace D2O): δ 8.46(d,1H);8.30(s,1H); 7.83(s,1H);7.81(s.1H);7.58(t,1); 7.33(t,1H);6.88(s,1H);4.65(m,1H);3.37 (m,1H);3.35(d,2H); 3.18 (m,1H); 2.98(m,2H); 2.65 (s,3H); 1.90(d,2H); 1.84(m,2H);1,28 (d,6H);1.17(d,6H). MS (ES^+): 602.2 $(M+1)^+$.

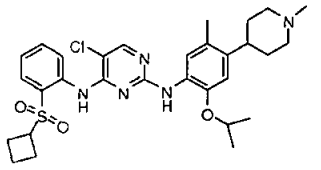
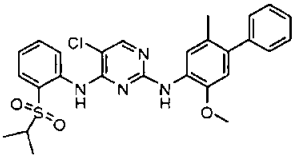
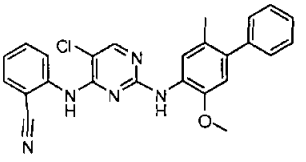
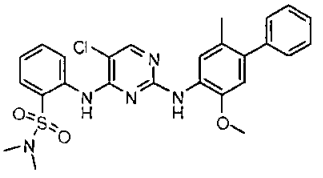
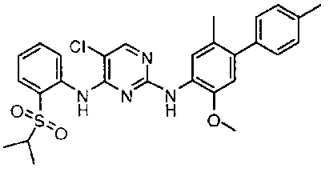
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
64	 5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-(morpholinomethyl)benzamide	1H NMR: (DMSO-d6 + trace D2O): δ 8.48(d,1H):8.36(s,1H); 8.27(s,1H); 7.82(dd,1H); 7.52 (m,1H); 7.36(d,1H); 7.33(s,1H); 4.76(m,1H); 4.39 (s, 2H); 4.01 (d,2H): 3.70(t.2H); 3.44 (m,1H); 3.36(d,2H); 3.19 (t.2H); 2.66(s, 3H);1.30(d,6H); 1.18(d,6H).MS (ES^+): 617.2 $(M+1)^+$.
65	 4-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-methylbenzoic acid	(TFA salt. CD3OD) δ 8.44 (d, 1H), 8.31 (s, 1H), 8.09 (s, 1H). 7.98 (d, 1H), 7.80 (dd, 1H), 7.59 (s, 1H), 7.45 (dd, 1H), 4.75-4.65 (m, 1H), 3.40-3.30 (m, 1H, partially obscured by CD3OD peak), 2.36 (s, 3H), 1.41 (d, 6H), 1.31 (d; 6H). MS (ES^+): 519.1 $(M+1)^+$.
66	 5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine	(HCl salt, DMSO-d6 + trace D2O) δ 8.32 (s, 1H), 8.27 (d, 1H), 7.88 (d, 1H), 7.67 (dd, 1H), 7.45 (dd, 1H), 7.42 (s, 1H), 6.79 (s, 1H), 4.56-4.48 (m, 1H), 3.49-3.32 (m, 3H), 3.10-2.91 (m, 3H), 2.09 (s, 3H), 1.89-1.77 (m, 4H), 1.22 (d, 6H), 1.13 (d, 6H). MS (ES^+): 558.1 $(M+1)^+$.
67	 5-chloro-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-[2-(propane-2-sulfonyl)phenyl]-pyrimidine-2,4-diamine	(HCl salt, DMSO-d6 + trace D2O) δ 8.28 (s, 1H), 8.19 (d, 1H). 7.86 (d, 1H), 7.66 (dd, 1H), 7.45 (dd, 1H), 7.37 (s, 1H), 6.77 (s, 1H), 4.56-4.49 (m, 1H), 3.51-3.37 (m, 3H), 3.16-3.08 (m, 2H), 2.98-2.88 (m, 1H), 2.77 (s, 3H), 2.05 (s, 3H), 1.90-1.81 (m, 4H), 1.19 (d, 6H), 1.11 (d, 6H). MS (ES^+): 572.2 $(M+1)^+$.

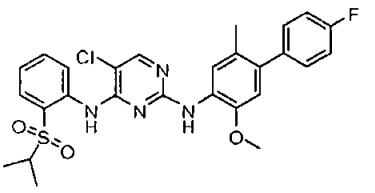
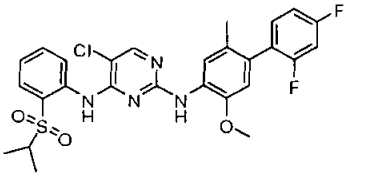
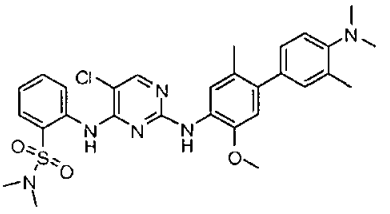
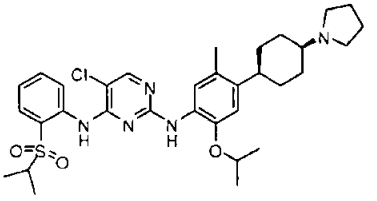
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
68	 (4-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-methylphenyl)(4-methylpiperazin-1-yl)methanone	MS (ES^+): 601.2 $(M+1)^+$.
69	 5-chloro-N2-(2-isopropoxy-5-methyl-4-(1-(1-methylpiperidin-4-yl)piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 655.3 $(M+1)^+$.
70	 5-chloro-N2-(2-isopropoxy-5-methyl-4-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 650.3 $(M+1)^+$.
71	 5-chloro-N2-(2-cyclobutoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine	MS (ES^+): 570.2 $(M+1)^+$.

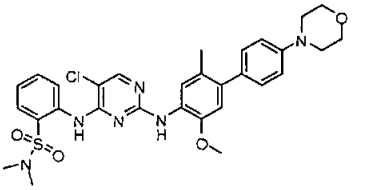
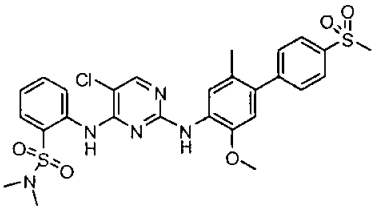
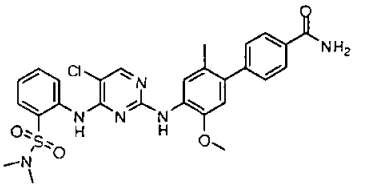
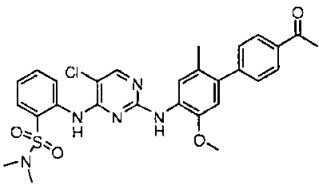
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
72	 2-[4-(4-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-methyl-phenyl)-piperidin-1-yl]-ethanol	MS (ES^+): 602.2 $(M+1)^+$.
73	 5-chloro-N2-(2-isopropoxy-4-(1-(2-methoxyethyl)piperidin-4-yl)-5-methylphenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 616.3 $(M+1)^+$.
74	 N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine	^{1}H NMR (HCl salt, DMSO-d6 + trace D2O, 400 MHz) 8.04 (s, 1H), 7.96 (dd, J = 8.0, 1.6 Hz, 2H), 7.79 (m, 1H), 7.61 (m, 1H), 7.27 (s, 1H), 6.81 (s, 1H), 4.55 (m, 1H), 3.43 (m, 3H), 3.08 (m, 2H), 2.91 (m, 1H), 2.77 (s, 3H), 2.17 (s, 3H), 1.98 (s, 3H), 1.91 (m, 2H), 1.80 (m, 2H), 1.24 (d, J = 6.0 Hz, 6H), 1.10 (d, J = 6.8 Hz, 6H). MS (ES^+): 552.7 $(M+1)^+$.
75	 5-chloro-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(propylsulfonyl)phenyl)pyrimidine-2,4-diamine	^{1}H NMR (HCl salt, CD_3OD, 400 MHz) 8.15 (s, 1H), 8.05 (m, 1H). 7.94 (dd, J = 8.0, 1.2 Hz, 1H), 7.66 (m, 1H). 7.50 (m, 1H), 7.19 (s, 1H), 6.83 (s, 1H), 4.60 (m, 1H), 3.54 (m, 2H), 3.13 (m, 4H), 2.99 (m, 1H), 2.82 (s, 3H), 2.06 (s, 3H), 1.91 (m, 4H), 1.54 (m, 2H), 1.19 (d, J = 2.0 Hz, 6H), 0.82 (t, J = 7.6 Hz, 3H). MS (ES^+): 572.2 $(M+1)^+$.MS (ES^+): 572.2 $(M+1)^+$.

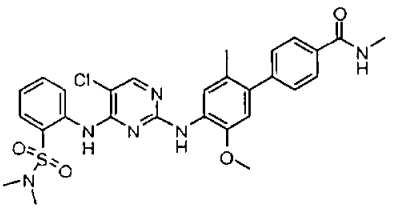
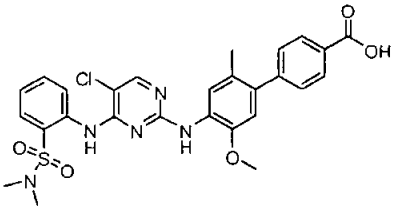
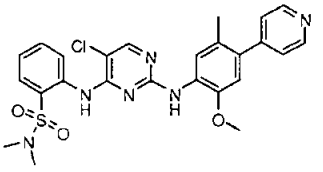
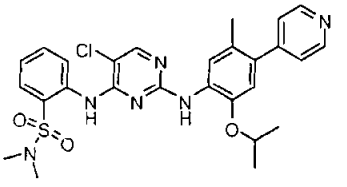
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
76	 2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide	^{1}H NMR (HCl salt, CD_3OD, 400 MHz) 8.14 (s, 1H), 8.09 (m, 1H), 7.86 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.59 (m, 1H), 7.44 (m, 1H), 7.24 (s, 1H), 6.83 (s, 1H), 4.59 (m, 1H), 3.51 (m, 2H), 3.13 (m, 2H), 3.02 (m, 1H), 2.82 (s, 3H), 2.62 (s, 6H), 2.09 (s, 3H), 1.92 (m, 4H), 1.19 (d, *J* = 6.0 Hz, 6H). MS (ES^+): 573.1 $(M+1)^+$.
77	 5-chloro-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(pyrrolidin-1-ylsulfonyl)phenyl)pyrimidine-2,4-diamine	^{1}H NMR (HCl salt, CD_3OD, 400 MHz) 8.14 (s, 1H). 8.09 (m, 1H), 7.89 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.58 (m, 1H), 7.40 (m, 1H), 7.28 (s, 1H), 6.83 (s, 1H), 4.59 (m, 1H), 3.51 (m, 2H), 3.13 (m, 6H), 3.02 (m, 1H), 2.82 (s, 3H), 2.09 (s, 3H), 1.91 (m, 4H), 1.67 (m, 4H), 1.20 (d, *J* = 6.0 Hz, 6H). MS (ES^+): 573.1 $(M+1)^+$.MS (ES^+): 599.3 $(M+1)^+$.
78	 5-chloro-N4-(2-(cyclobutylaminosulfonyl)phenyl)-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)pyrimidine-2,4-diamine	^{1}H NMR (HCl salt, CD_3OD, 400 MHz) 8.17 (s, 1H), 8.05 (m, 1H), 7.89 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.56 (m, 1H), 7.38 (m, 1H), 7.28 (s, 1H), 6.84 (s, 1H), 4.61 (m, 1H), 3.59 (m, 1H), 3.51 (m, 2H), 3.14 (m, 2H), 3.00 (m, 1H), 2.82 (s, 3H), 2.07 (s, 3H), 1.91 (m, 6H), 1.67 (m, 2H), 1.36 (m, 2H), 1.20 (d, *J* = 6.0 Hz, 6H). MS (ES^+): 599.3 $(M+1)^+$.
79	 2-(2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)-5-chloropyrimidin-4-ylamino)-N,N-dimethylbenzamide	^{1}H NMR (HCl salt, CD_3OD, 400 MHz) 8.15 (s, 1H), 7.78 (m, 1H), 7.59 (m, 1H), 7.54 (m, 1H), 7.46 (m, 1H), 7.33 (s, 1H), 6.90 (s, 1H), 4.69 (m, 1H), 3.61 (m, 2H), 3.22 (m, 2H), 3.09 (m, 1H), 3.06 (s, 3H), 2.92 (s, 6H), 2.17 (s, 3H), 2.00 (m, 4H), 1.30 (d, *J* = 6.0 Hz, 6H). MS (ES^+): 537.3 $(M+1)^+$.

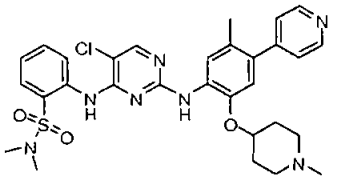
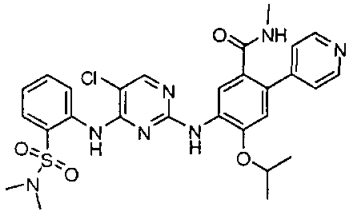
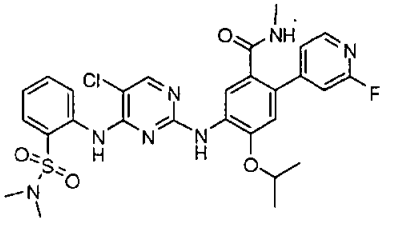
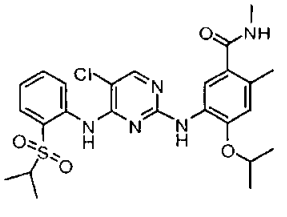
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
80	 2-(2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)-5-chloropyrimidin-4-ylamino) benzamide	^{1}H NMR (HCl salt, CD_3OD, 400 MHz) 8.60 (s, 1H), 8.15 (s, 1H), 7.88 (m, 1H), 7.48 (m, 1H), 7.44 (m, 1H), 7.33 (m, 1H), 6.99 (s, 1H), 4.69 (m, 1H), 3.64 (m, 2H). 3.28 (m, 3H), 2.95 (s, 3H), 2.32 (s, 3H), 2.08 (m. 4H), 1.30 (d, J = 6.0 Hz, 6H). MS (ES^+): 509.2 $(M+1)^+$.
81	 5-chloro-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(aminosulfonyl)phenyl)pyrimidine-2,4-diamine	^{1}H NMR (HCl salt, CD_3OD, 400 MHz) 8.12 (s, 1H), 8.09 (s, 1H), 7.94 (dd, J = 8.0, 1.6 Hz, 1H), 7.52 (m, 1H), 7.36 (m, 1H), 7.28 (s, 1H), 6.85 (s, 1H), 4.60 (m, 1H), 3.51 (m, 2H), 3.09 (m, 2H), 3.02 (m, 1H), 2.82 (s, 3H), 2.11 (s, 3H), 1.92 (m, 4H), 1.19 (d, J = 6.0 Hz, 6H).MS (ES^+): 545.2 $(M+1)^+$.
82	 5-chloro-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(methylsulfonyl)phenyl)pyrimidine-2,4-diamine	^{1}H NMR (HCl salt, CD_3OD, 400 MHz) 8.14 (s, 1H), 8.04 (s, 1H), 8.00 (dd, J = 8.0, 1.6 Hz, 1H), 7.67 (m, 1H), 7.49 (m, 1H), 7.23 (s, 1H), 6.82 (s, 1H), 4.58 (m, 1H), 3.54 (m, 2H), 3.14 (m, 2H), 3.10 (s, 3H), 3.00 (m, 1H), 2.82 (s, 3H), 2.08 (s, 3H), 1.89 (m, 4H), 1.19 (d, J = 6.0 Hz, 6H). MS (ES^+): 544.2 $(M+1)^+$.
83	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(aminosulfonyl)phenyl)pyrimidine-2,4-diamine	^{1}H NMR (HCl salt, DMSO-d6, 400 MHz) 9.61 (s, 1H), 9.39 (s, 1H), 9.11 (s, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.23 (s, 1H), 7.84 (dd, J = 8.0, 1.6 Hz, 1H), 7.70 (s, 2H), 7.41 (m, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.20 (m, 1H), 7.00 (d, J = 12.4 Hz, 1H), 3.52 (m, 2H), 3.11 (m, 2H), 2.99 (m, 1H), 2.82 (d, J = 4.8 Hz, 3H), 2.25 (s, 3H), 1.92 (m, 2H), 1.81(m, 2H). MS (ES^+): 505.2 $(M+1)^+$.

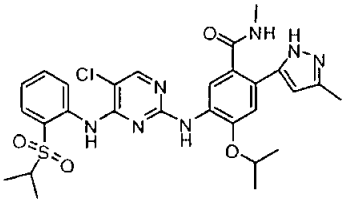
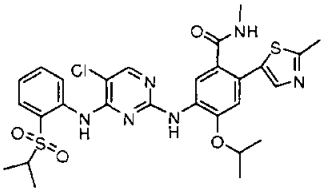
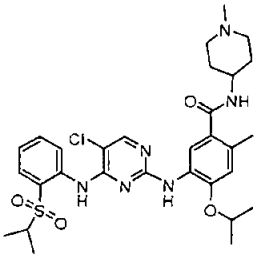
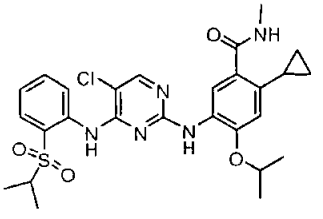
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
84	 5-chloro-N4-(2-(cyclobutylsulfonyl)phenyl)-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)pyrimidine-2,4-diamine	^{1}H NMR (HCl salt, CD_3OD, 400 MHz) 8.15 (s, 1H), 8.07 (s, 1H), 7.92 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.65 (m, 1H), 7.47 (m, 1H), 7.20 (s, 1H), 6.84 (s, 1H), 4.58 (m, 1H), 3.99 (m, 1H). 3.52 (m, 2H), 3.14 (m. 2H), 3.02 (m, 1H), 2.83 (s, 3H), 2.35 (m, 2H), 2.08 (s, 3H), 2.00 (m, 2H),1.89 (m, 6H), 1.19 (d, *J* = 6.0 Hz, 6H). MS (ES^+): 584.2 $(M+1)^+$.
85	 5-chloro-N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methoxy-5-methyl-4-phenyl)-phenyl)pyrimidine-2,4-diamine	MS (ES^+): 523.2 $(M+1)^+$.
86	 5-chloro-N4-(2-cyanophenyl)-N2-(2-methoxy-5-methyl-4-phenyl)-phenyl)pyrimidine-2,4-diamine	MS (ES^+): 442.1 $(M+1)^+$.
87	 2-(5-chloro-2-(5-methoxy-2-methylbiphenyl-4-ylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide	MS (ES^+): 524.1 $(M+1)^+$.
88	 5-chloro-N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methoxy-5-methyl-4-(4-methylphenyl)-phenyl)pyrimidine-2,4-diamine	MS (ES^+): 537.0 $(M+1)^+$.

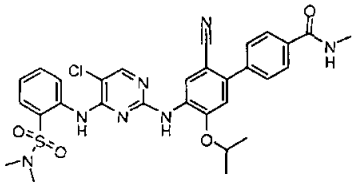
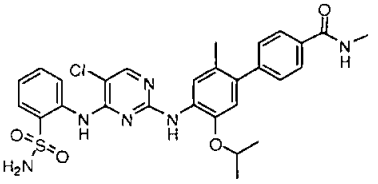
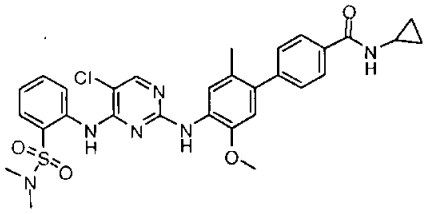
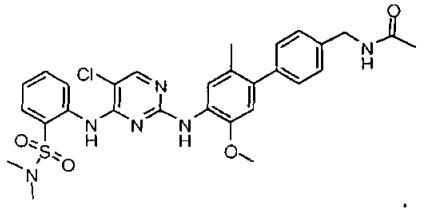
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
89	 5-chloro-N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methoxy-5-methyl-4-(4-fluorophenyl)-phenyl)pyrimidine-2,4-diamine	MS (ES^+): 541.1 $(M+1)^+$.
90	 5-chloro-N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methoxy-5-methyl-4-(2,4-difluorophenyl)-phenyl)pyrimidine-2,4-diamine	MS (ES^+): 559.0 $(M+1)^+$.
91	 2-(5-chloro-2-(4'-(dimethylamino)-5-methoxy-2,3'-dimethylbiphenyl-4-ylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide	MS (ES^+): 581.2 $(M+1)^+$.
92	 5-chloro-N2-(2-isopropoxy-5-methyl-4-((1s,4s)-4-(pyrrolidin-1-yl)cyclohexyl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 626.3 $(M+1)^+$.

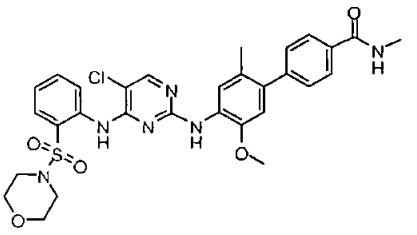
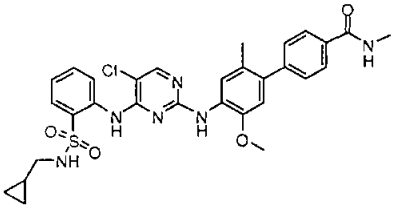
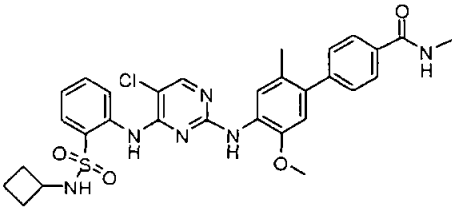
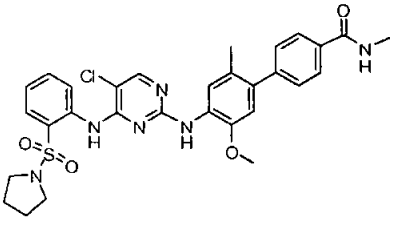
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
93	 2-(5-chloro-2-(5-methoxy-2-methyl-4'-morpholinobiphenyl-4-ylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide	MS (ES^+): 609.2 $(M+1)^+$.
94	 2-(5-chloro-2-(5-methoxy-2-methyl-4'-(methylsulfonyl)biphenyl-4-ylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide	MS (ES^+): 602.1 $(M+1)^+$.
95	 4'-(5-chloro-4-(2-(N,N-dimethylsulfamoyl) phenylamino)pyrimidin-2-ylamino)-5'-methoxy-2'-methylbiphenyl-4-carboxamide	MS (ES^+): 567.2 $(M+1)^+$.
96	 2-(2-(4'-acetyl-5-methoxy-2-methylbiphenyl-4-ylamino)-5-chloropyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide	MS (ES^+): 566.2 $(M+1)^+$.

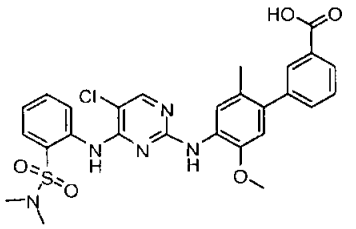
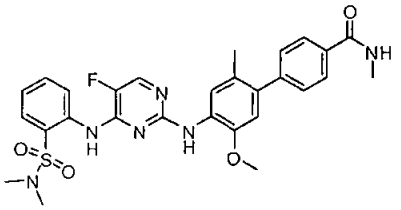
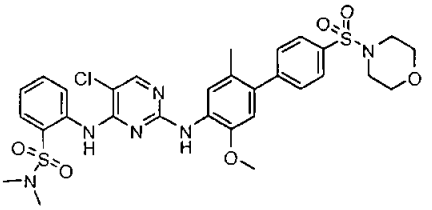
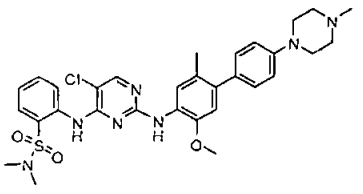
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
97	 4'-(5-chloro-4-(2-(N,N-dimethylsulfamoyl) phenylamino)pyrimidin-2-ylamino)-5'-methoxy-N,2'-dimethylbiphenyl-4-carboxamide	MS (ES^+): 581.2 $(M+1)^+$.
98	 4'-(5-chloro-4-(2-(N,N-dimethylsulfamoyl) phenylamino)pyrimidin-2-ylamino)-5'-methoxy-2'-methylbiphenyl-4-carboxylic acid	MS (ES^+): 568.1 $(M+1)^+$.
99	 2-(5-chloro-2-(2-methoxy-5-methyl-4-(pyridin-4-yl)phenylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide	MS (ES^+): 525.1 $(M+1)^+$.
100	 2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(pyridin-4-yl)phenylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide	MS (ES^+): 553.2 $(M+1)^+$.

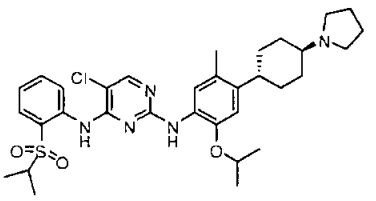
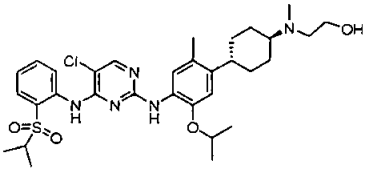
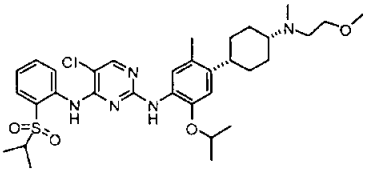
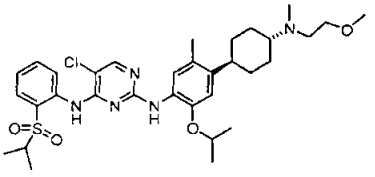
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
101	 2-(5-chloro-2-(5-methyl-2-(1-methylpiperidin-4-yloxy)-4-(pyridin-4-yl)phenylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide	MS (ES^+): 608.2 $(M+1)^+$.
102	 5-(5-chloro-4-(2-(N,N-dimethylsulfamoyl) phenylamino)pyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-(pyridin-4-yl)benzamide	MS (ES^+): 596.2 $(M+1)^+$.
103	 5-(5-chloro-4-(2-(N,N-dimethylsulfamoyl) phenylamino)pyrimidin-2-ylamino)-2-(2-fluoropyridin-4-yl)-4-isopropoxy-N-methylbenzamide	MS (ES^+): 614.2 $(M+1)^+$.
104	 5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N,2-dimethylbenzamide	MS (ES^+): 532.0 $(M+1)^+$.

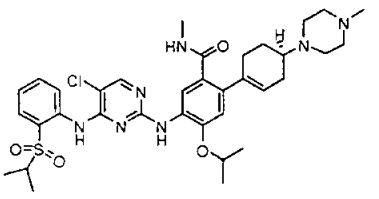
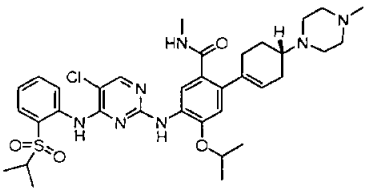
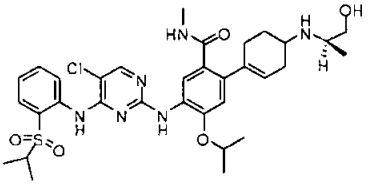
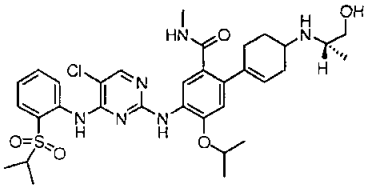
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
105	 5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-(3-methyl-1H-pyrazol-5-yl)benzamide	MS (ES^+): 598.2 $(M+1)^+$.
106	 5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-(2-methylthiazol-5-yl)benzamide	MS (ES^+): 615.2 $(M+1)^+$.
107	 5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-2-methyl-N-(1-methylpiperidin-4-yl)benzamide	MS (ES^+): 615.2 $(M+1)^+$.
108	 5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2-cyclopropyl-4-isopropoxy-N-methylbenzamide	MS (ES^+): 558.2 $(M+1)^+$.

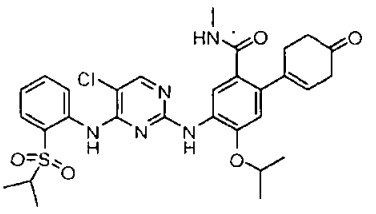
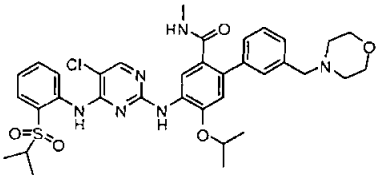
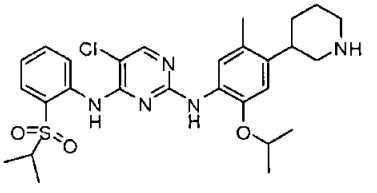
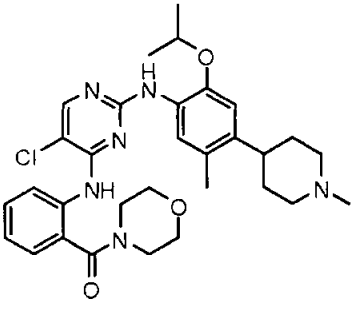
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
109	 4'-(5-chloro-4-(2-(N,N-dimethylsulfamoyl) phenylamino)pyrimidin-2-ylamino)-2'-cyano-5'-isopropoxy-N-methylbiphenyl-4-carboxamide	MS (ES^+): 620.2 $(M+1)^+$.
110	 5-chloro-N4-(2-(sulfonylamino)phenyl)-N2-(2-methoxy-5-methyl-4-(3-methyl-4-(methylacetamidophenyl)-phenyl)pyrimidine-2,4-diamine	MS (ES^+): 581.2 $(M+1)^+$.
111	 4'-(5-chloro-4-(2-(N,N-dimethylsulfamoyl) phenylamino)pyrimidin-2-ylamino)-N-cyclopropyl-5'-methoxy-2'-methylbiphenyl-4-carboxamide	MS (ES^+): 607.2 $(M+1)^+$.
112	 N-((4'-(5-chloro-4-(2-(N,N-dimethylsulfamoyl) phenylamino)pyrimidin-2-ylamino)-5'-methoxy-2'-methylbiphenyl-4-yl)methyl)acetamide	MS (ES^+): 595.2 $(M+1)^+$.

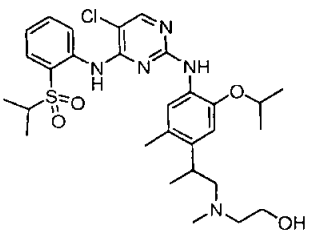
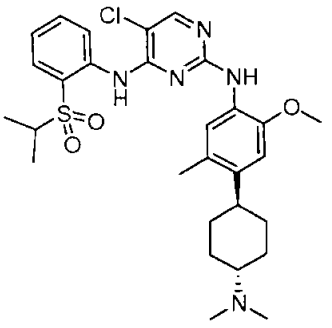
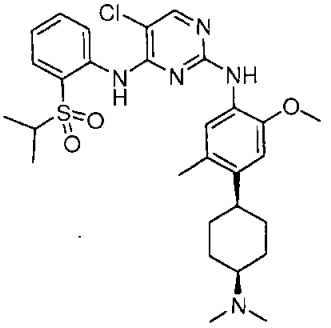
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
113	 5-chloro-N4-(2-(morpholinosulfonyl)phenyl)-N2-(2-methoxy-5-methyl-4-(4-(methylacetamidophenyl)-phenyl)pyrimidine-2,4-diamine	MS (ES^+): 623.2 $(M+1)^+$.
114	 4'-(5-chloro-4-(2-(N-(cyclopropylmethyl) sulfamoyl)phenylamino)pyrimidin-2-ylamino)-5'-methoxy-N,2'-dimethylbiphenyl-4-carboxamide	MS (ES^+): 607.1 $(M+1)^+$.
115	 4'-(5-chloro-4-(2-(N-cyclobutylsulfamoyl) phenylamino)pyrimidin-2-ylamino)-5'-methoxy-N,2'-dimethylbiphenyl-4-carboxamide	MS (ES^+): 607.1 $(M+1)^+$.
116	 5-chloro-N4-(2-(pyrrolidinosulfonyl)phenyl)-N2-(2-methoxy-5-methyl-4-(4-acetamidomethylphenyl)-phenyl)pyrimidine-2,4-diamine	MS (ES^+): 607.2 $(M+1)^+$.

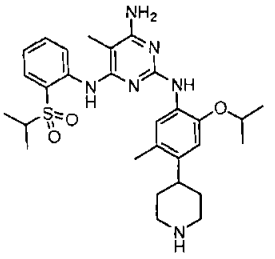
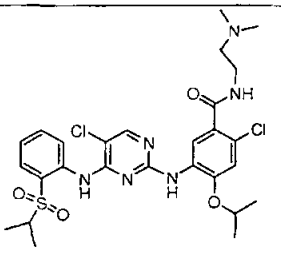
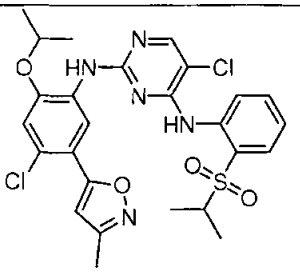
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
117	 4'-(5-chloro-4-(2-(N,N-dimethylsulfamoyl) phenylamino)pyrimidin-2-ylamino)-5'-methoxy-2'-methylbiphenyl-3-carboxylic acid	MS (ES^+): 568.1 $(M+1)^+$.
118	 4'-(4-(2-(N,N-dimethylsulfamoyl)phenylamino)-5-fluoropyrimidin-2-ylamino)-5'-methoxy-N,2'-dimethylbiphenyl-4-carboxamide	MS (ES^+): 565.2 $(M+1)^+$.
119	 2-(5-chloro-2-(5-methoxy-2-methyl-4'-(morpholinosulfonyl)biphenyl-4-ylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide	MS (ES^+): 673.2 $(M+1)^+$.
120	 2-(5-chloro-2-(5-methoxy-2-methyl-4'-(4-methylpiperazin-1-yl)biphenyl-4-ylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide	MS (ES^+): 622.2 $(M+1)^+$.

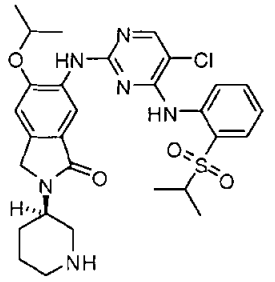
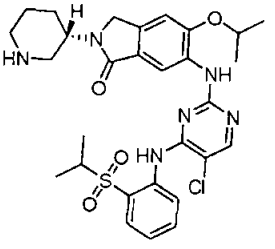
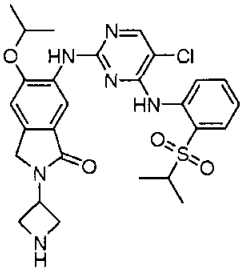
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
121	 5-chloro-N2-(2-isopropoxy-5-methyl-4-((1r,4r)-4-(pyrrolidin-1-yl)cyclohexyl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 626.3 $(M+1)^+$.
122	 2-(N-((1r,4r)-4-(4-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-methylphenyl)cyclohexyl)-N-methylamino)ethanol	MS (ES^+): 630.3 $(M+1)^+$.
123	 N2-(4-((1s,4s)-4-(N-(2-methoxyethyl)-N-methylamino)cyclohexyl)-2-isopropoxy-5-methylphenyl)-5-chloro-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine	MS (ES^+): 644.3 $(M+1)^+$.
124	 N2-(4-((1r,4r)-4-(N-(2-methoxyethyl)-N-methylamino)cyclohexyl)-2-isopropoxy-5-methylphenyl)-5-chloro-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 644.3 $(M+1)^+$.

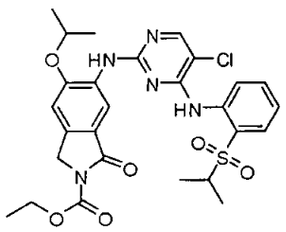
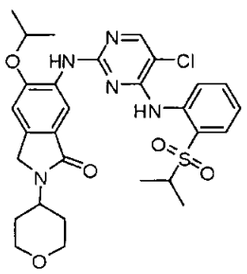
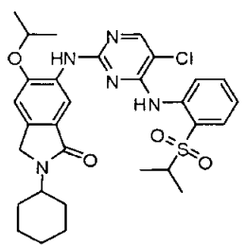
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
125	 5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-((R)-4-(4-methylpiperazin-1-yl)cyclohex-1-enyl)benzamide	MS (ES^+): 696.3 $(M+1)^+$.
126	 5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-((S)-4-(4-methylpiperazin-1-yl)cyclohex-1-enyl)benzamide	MS (ES^+): 696.3 $(M+1)^+$.
127	 2-(4-((R)-1-hydroxypropan-2-ylamino)cyclohex-1-enyl)-5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methylbenzamide	MS (ES^+): 671.3 $(M+1)^+$.
128	 2-(4-((S)-1-hydroxypropan-2-ylamino)cyclohex-1-enyl)-5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methylbenzamide	MS (ES^+): 671.3 $(M+1)^+$.

	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
129	 5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-(4-oxocyclohex-1-enyl)benzamide	MS (ES^+): 612.2 $(M+1)^+$.
130	 5-chloro-N4-(2-(isopropylsulfony)phenyl)-N2-(2-isopropoxy-5-(N-methylcarboxamido)-4-(3-methyl-4-(3-morpholinomethyl)-phenyl)pyrimidine-2,4-diamine	MS (ES^+): 693.3 $(M+1)^+$.
131	 5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-3-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine	MS (ES^+): 558.2 $(M+1)^+$.
132	 (2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)phenyl)(morpholino)methanone	MS (ES^+): 579.1 $(M+1)^+$.

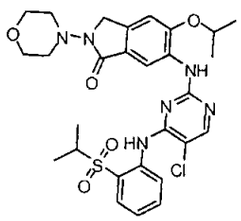
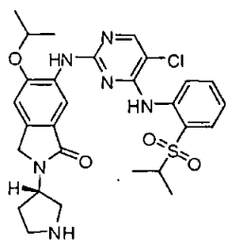
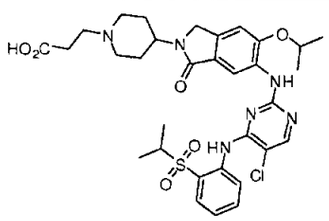
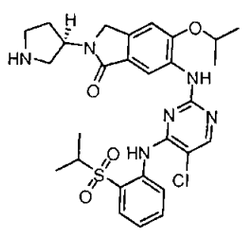
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
133	 2-((2-(4-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyrimidin-2-ylamino)-5-isopropoxy-2-methylphenyl) propyl)(methyl)amino)ethanol	MS (ES$^+$): 590.1 $(M+1)^+$.
134	 5-chloro-N2-(4-((1r,4r)-4-(dimethylamino) cyclohexyl)-2-methoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine	MS (ES$^+$): 572.1 $(M+1)^+$.
135	 5-chloro-N2-(4-((1s,4s)-4-(dimethylamino) cyclohexyl)-2-methoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine	MS (ES$^+$): 572.1 $(M+1)^+$.

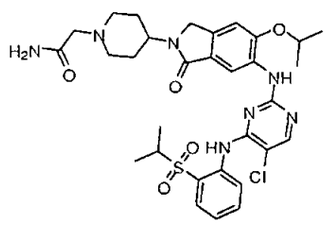
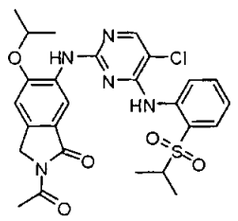
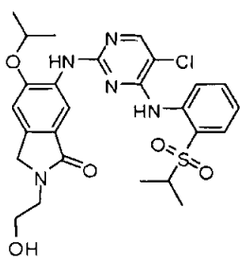
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
136	 N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-5-methylpyrimidine-2,4,6-triamine	MS (ES^+): 552.7 $(M+1)^+$.
137	 5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2-chloro-N-(2-(dimethylamino)ethyl)-4-isopropoxybenzamide	MS (ES^+): 610.0 $(M+1)^+$.
138	 5-chloro-N2-(4-chloro-2-isopropoxy-5-(3-methylisoxazol-5-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 577.5 $(M+1)^+$.

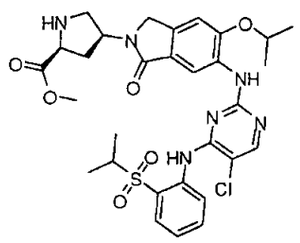
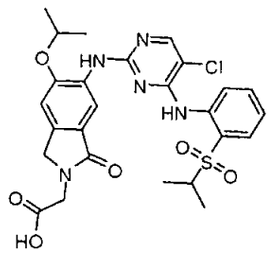
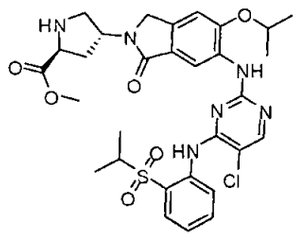
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
139	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-((R)-piperidin-3-yl)isoindolin-1-one	MS (ES^+): 599.2 $(M+1)^+$.
140	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-((S)-piperidin-3-yl)isoindolin-1-one	MS (ES^+): 599.2 $(M+1)^+$.
141	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2-(azetidin-3-yl)-5-isopropoxyisoindolin-1-one	MS (ES^+): 571.2 $(M+1)^+$.

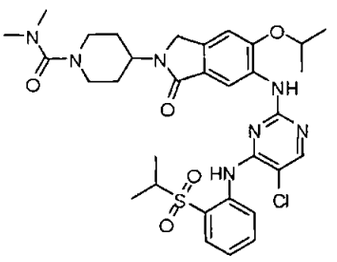
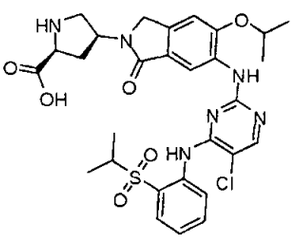
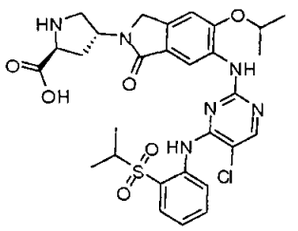
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
142	 Ethyl 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindoline-2-carboxylate	MS (ES^+): 588.2 $(M+1)^+$.
143	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2-(tetrahydro-2H-pyran-4-yl)-5-isopropoxyisoindolin-1-one	MS (ES^+): 600.2 $(M+1)^+$.
144	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloro pyrimidin-2-ylamino)-2-cyclohexyl-5-isopropoxy-isoindolin-1-one	MS (ES^+): 598.2 $(M+1)^+$.

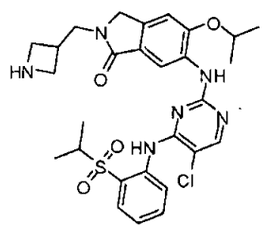
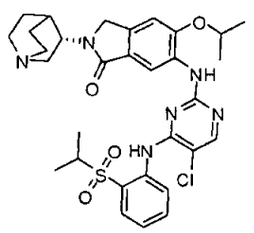
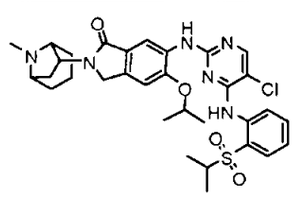
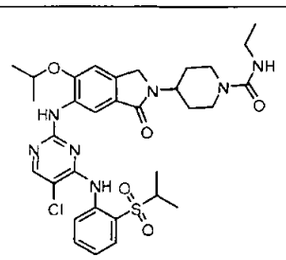
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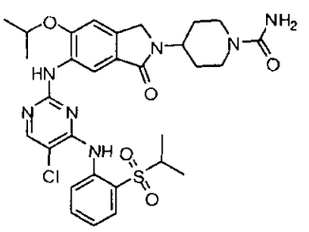
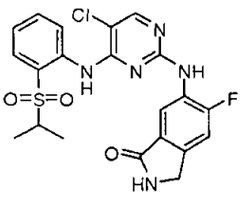
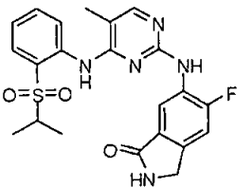
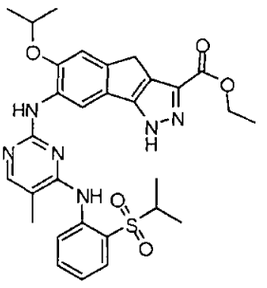
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
145	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloro pyrimidin-2-ylamino)-5-isopropoxy-2-morpholino-isoindolin-1-one	MS (ES^+): 601.2 $(M+1)^+$.
146	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-((S)-pyrrolidin-3-yl)isoindolin-1-one	MS (ES^+): 585.2 $(M+1)^+$.
147	 3-(4-(6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)piperidin-1-yl)propanoic acid	MS (ES^+): 671.2 $(M+1)^+$.
148	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-((R)-pyrrolidin-3-yl)isoindolin-1-one	MS (ES^+): 585.2 $(M+1)^+$.

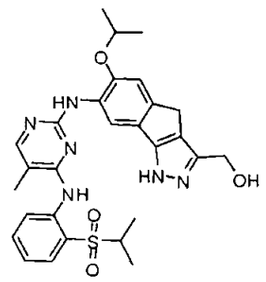
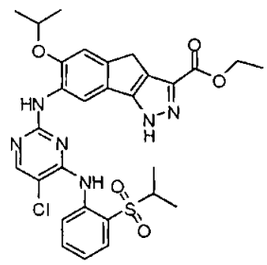
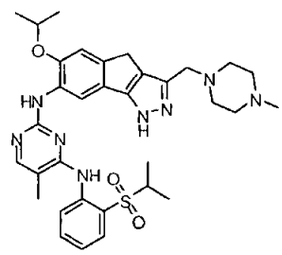
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
149	 2-[4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenyl-amino]-pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidin-1-yl]-acetamide	MS (ES^+): 656.2 $(M+1)^+$.
150	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2-acetyl-5-isopropoxyisoindolin-1-one	MS (ES^+): 558.2 $(M+1)^+$.
151	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2-(2-hydroxyethyl)-5-isopropoxyisoindolin-1-one	MS (ES^+): 560.2$(M+1)^+$.

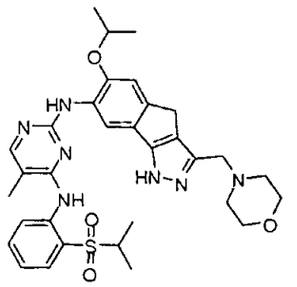
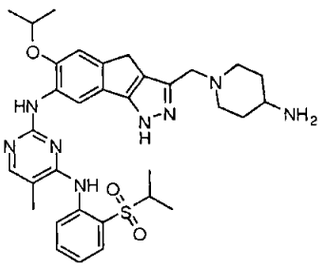
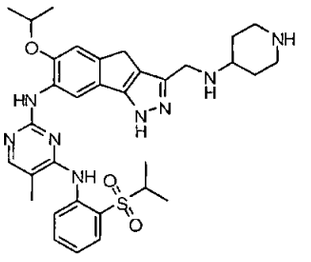
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
152	 (2S,4S)-methyl 4-(6-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)pyrrolidine-2-carboxylate	MS (ES^+): 643.2 $(M+1)^+$.
153	 2-(6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)acetic acid	MS (ES^+): 574.1 $(M+1)^+$.
154	 (2S,4R)-methyl 4-(6-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)pyrrolidine-2-carboxylate	MS (ES^+): 643.2 $(M+1)^+$.

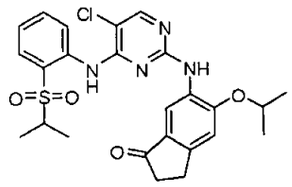
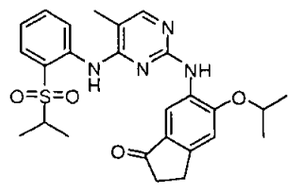
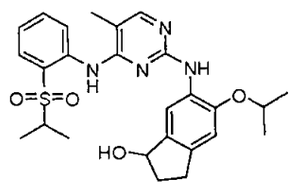
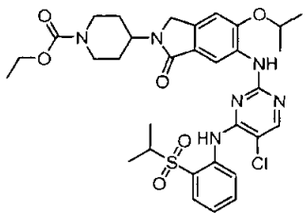
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
155	 4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid dimethylamide	^{1}H NMR (400 MHz, MeOD-d_4) δ 8.29 (s, 1H), 8.26 (br, 1H), 7.96 (dd, 1H), 7.93 (s, 1H), 7.72(dd, 1H), 7.48 (dd, 1H), 7.35 (s, 1H), 4.50 (s, 2H), 4.35-4.29 (m, 1H), 3.83 (d, 2H), 3.38-3.30 (m, 2H), 3.02-2.95 (m, 3H), 2.88 (s, 6H), 1.88-1.84 (m, 3H), 1.36 (d, 6H), 1.25 (d, 6H); ESMS *m/z* 670.2 (M + H^+).
156	 (2S,4S)-4-(6-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)pyrrolidine-2-carboxylic acid	MS (ES^+): 629.2 $(M+1)^+$.
157	 (2S,4R)-4-(6-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)pyrrolidine-2-carboxylic acid	MS (ES^+): 629.2 $(M+1)^+$.

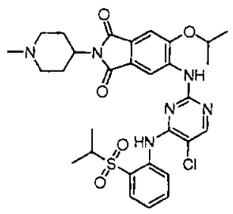
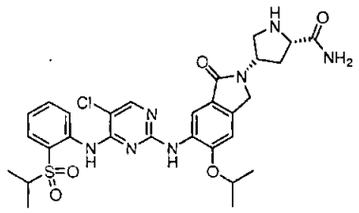
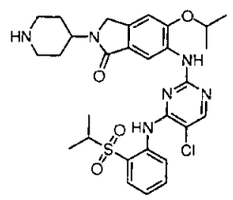
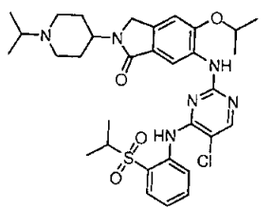
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
158	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2-((azetidin-3-yl)methyl)-5-isopropoxyisoindolin-1-one	MS (ES^+): 585.2 $(M+1)^+$.
159	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-((S)-quinuclidin-3-yl)isoindolin-1-one	MS (ES^+): 625.2 $(M+1)^+$.
160	 6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-yl)-2,3-dihydro-isoindol-1-one	MS (ES^+): 639.2 $(M+1)^+$.
161	 4-(6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)-N-ethylpiperidine-1-carboxamide	MS (ES^+): 670.3 $(M+1)^+$.

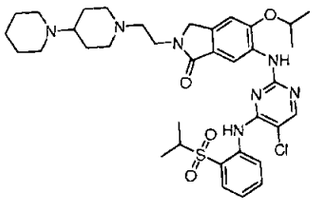
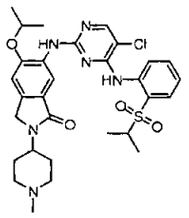
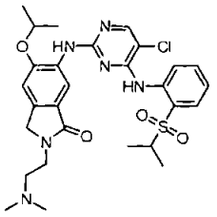
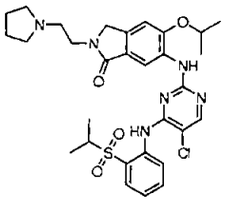
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
162	 4-(6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)piperidine-1-carboxamide	MS (ES^+): 642.1 $(M+1)^+$.
163	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-fluoroisoindolin-1-one	MS (ES^+): 476.1 $(M+1)^+$.
164	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-methylpyrimidin-2-ylamino)-5-fluoroisoindolin-1-one	MS (ES^+): 456.1 $(M+1)^+$.
165	 Ethyl 7-(4-(2-(isopropylsulfonyl)phenylamino)-5-methylpyrimidin-2-ylamino)-1,4-dihydro-6-isopropoxyindeno[1,2-c]pyrazole-3-carboxylate	MS (ES^+): 591.2 $(M+1)^+$.

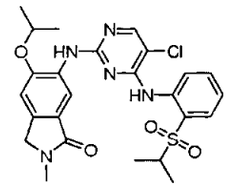
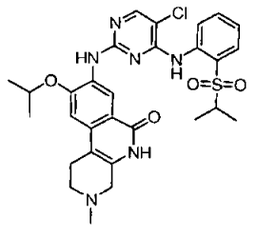
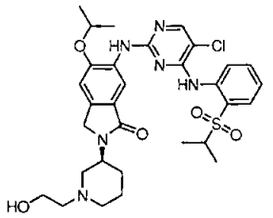
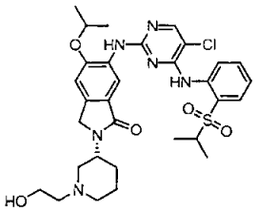
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
166	 (7-(4-(2-(isopropylsulfonyl)phenylamino)-5-methylpyrimidin-2-ylamino)-1,4-dihydro-6-isopropoxyindeno[1,2-c]pyrazol-3-yl)methanol	MS (ES^+): 549.2 $(M+1)^+$.
167	 Ethyl 7-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-1,4-dihydro-6-isopropoxyindeno[1,2-c]pyrazole-3-carboxylate	MS (ES^+): 611.2 $(M+1)^+$.
168	 N2-(1,4-dihydro-6-isopropoxy-3-((4-methylpiperazin-1-yl)methyl)indeno[1,2-c]pyrazol-7-yl)-N4-(2-(isopropylsulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine	MS (ES^+): 631.3 $(M+1)^+$.

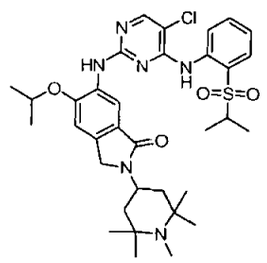
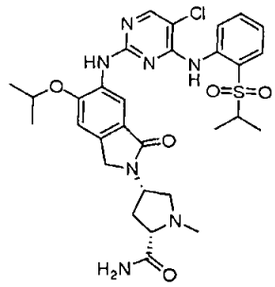
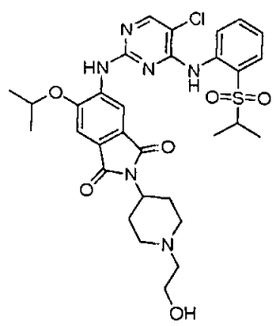
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
169	 N2-(1,4-dihydro-6-isopropoxy-3-(morpholinomethyl) indeno[1,2-c]pyrazol-7-yl)-N4-(2-(isopropylsulfonyl) phenyl)-5-methylpyrimidine-2,4-diamine	MS (ES^+): 618.3 $(M+1)^+$.
170	 N2-(3-((4-aminopiperidin-1-yl)methyl)-1,4-dihydro-6-isopropoxyindeno[1,2-c]pyrazol-7-yl)-N4-(2-(isopropylsulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine	MS (ES^+): 631.3 $(M+1)^+$.
171	 N2-(1,4-dihydro-6-isopropoxy-3-((piperidin-4-ylamino)methyl)indeno[1,2-c]pyrazol-7-yl)-N4-(2-(isopropylsulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine	MS (ES^+): 631.3 $(M+1)^+$.

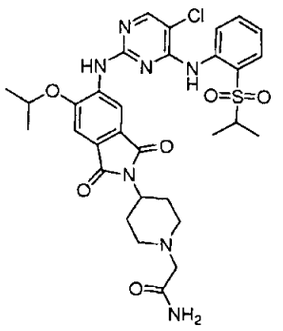
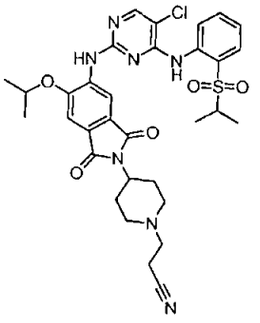
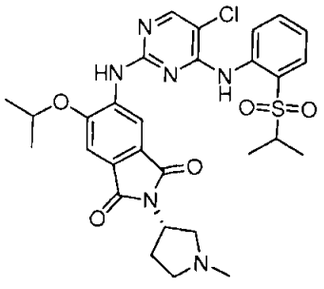
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
172	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2,3-dihydro-5-isopropoxyinden-1-one	MS (ES^+): 515.1 $(M+1)^+$.
173	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-methylpyrimidin-2-ylamino)-2,3-dihydro-5-isopropoxyinden-1-one	MS (ES^+): 495.2 $(M+1)^+$.
174	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-methyl pyrimidin-2-ylamino)-2,3-dihydro-5-isopropoxy-1H-inden-1-ol	MS (ES^+): 497.2 $(M+1)^+$.
175	 4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino] -pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro -isoindol-2-yl)-piperidine-1-carboxylic acid ethyl ester	^{1}H NMR 400 MHz (DMSO-d_6 with trace D_2O) δ 8.55 (d, 1H), 8.32 (s, 1H), 8.14 (s, 1H), 7.82 (dd,1H), 7.74 (t, 1H), 7.34 (t, 1H), 7.28 (s, 1H), 4.73 (m, 2H), 4.39 (s, 2H), 4.12 (m, 2H), 4.06 (q, 2H), 3.46 (m, 1H), 2.92 (m 2H), 1.76 (m, 2H), 1.68 (m, 2H), 1.29 (d, 6H), 1.20 (t, 3H), 1.17 (d, 6H); MS m/z 671 (M+1).

	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
176	 5-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-6-isopropoxy-2-(1-methyl-piperidin-4-yl)-isoindole-1,3-dione	^{1}H NMR 400 MHz (DMSO-d_6 with trace D_2O) δ 8.44 (s, 2H), 8.39 (s, 1H), 7.87 (dd, 1H), 7.78 (dt, 1H), 7.45 (s, 1H), 7.41 (m, 1H), 4.91(m, 2H), 4.25(m, 2H), 3.51 (m, 3H), 3.10(m, 2H), 2.77(s, 3H), 1.80(m, 2H), 1.35(d, 6H), 1.13(d, 6H); MS m/z 627 (M+1).
177	 *(2S. 4S)*-4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro-isoindol-2-yl)-pyrrolidine-2-carboxylic acid amide	^{1}H NMR 400 MHz (DMSO-d_6 with trace D_2O) δ 8.47(d, 1H), 8.25 (s, 1H), 8.07 (s, 1H), 7.78 (dd, 1H), 7.68 (m, 1H), 7.31(t, 1H), 7,24 (s, 1H), 4,71 (m, 2H), 4.43 (dd, 2H), 3.60 (m, 1H), 3.44 (m, 1H), 3.35 (m,1H), 2.63 (m, 1H), 2.28 (m, 1H), 1.22 (d, 6H), 1.10 (d, 6H); MS m/z 628 (M+1).
178	 6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-piperidin-4-yl-2,3-dihydro-isoindol-1-one	^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 10.13 (s, 1H), 9.60-9.50 (br, 1H), 9.34-9.21 (br, 1H), 8.46 (d, 1H), 8.26 (s, 1H), 8.08 (s, 1H), 7.91 (dd, 1H), 7.71 (m, 1H), 7.34 (t, 1H), 7.03 (s, 1H), 4.30 (m, 1H), 4.53 (m, 1H), 4.33 (s, 2H), 3.62 (m, 2H), 3.21-3.09 (m, 3H), 2.31-2.21 (m, 2H), 2.09-2.05 (m, 2H), 1.41 (d, 6H), 2.30 (d, 6H); ESMS *m/z* 599.2 ($M + H^+$).
179	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-(1-isopropylpiperidin-4-yl)isoindolin-1-one	MS (ES^+): 641.3 $(M+1)^+$.

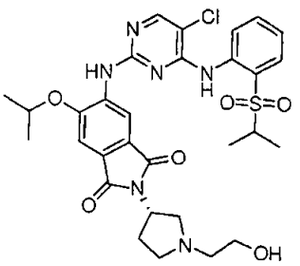
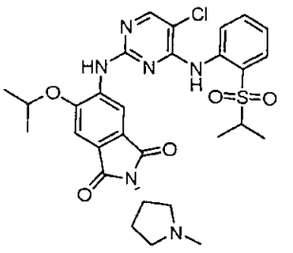
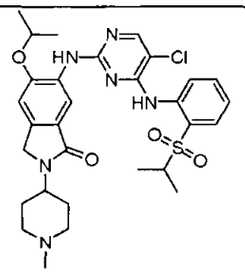
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
180	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-(2-(4-(piperidin-1-yl)piperidin-1-yl)ethyl)isoindolin-1-one	MS (ES^+): 710.3 $(M+1)^+$.
181	 6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-(1-methyl-piperidin-4-yl)-2,3-dihydro-isoindol-1-one	^{1}H NMR 400 MHz (DMSO-d_6 with trace D_2O) δ 8.46 (d, 1H), 8.35 (s, 1H), 8.09(s, 1H), 7.82(d, 1H), 7.74(t, 1H), 7.36(t,1H), 7.33(s, 1H), 4.75 (m, 1H), 4.41(s, 2H), 4,29(m, 1H), 3.65(m, 2H), 3.44(m, 1H), 3.17(t, 2H), 2,79(s, 3H), 2.07(m, 2H), 1,98(d, 2H), 1.28(d, 6H), 1.14(d, 6H); MS m/z 613 (M+1).
182	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloro pyrimidin-2-ylamino)-2-(1-(2-(dimethylamino)ethyl) piperidin-4-yl)-5-isopropoxyisoindolin-1-one	8.60(d,1H), 8.33(s,1H);8.20 (s,1H):7.82(dd,1H);7.77(dt, 1H); 7.35(s, 1H); 7.33(t,1H): 4.76 (m, 1H); 4.44(s,2H); 3.88 (t, 2H); 3.40 (m, 3H); 2.87 (s, 6H); 1,30 (d, 6H); 1.16 (d, 6H).). MS (ES^+): 587.2 $(M+1)^+$.
183	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-(1-(2-(pyrrolidin-1-yl)ethyl)piperidin-4-yl)isoindolin-1-one	8.60(d,1H): 8.32(s,1H):8.20 (s, 1H);7.83(dd,1H);7.78 (dt,1H);7.35 (s,1H):7.31(t,1H):4.76(m,1H);4.46(s,2H);3.87 (t,2H); 3.63 (m,2H); 3.48 (m,1H); 3.09 (m,2H): 2.05 (m, 2H); 1.85 (m, 2H): 1.30(d,6H): 1.17(d,6H). MS (ES^+): 613.2 $(M+1)^+$.

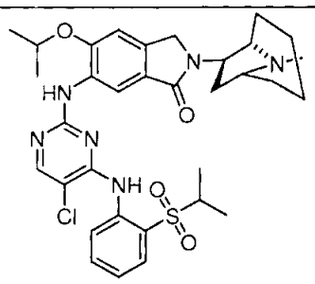
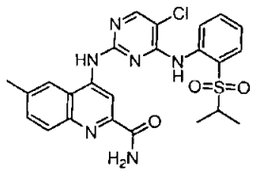
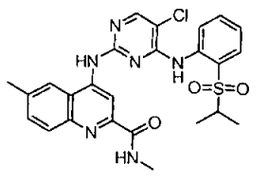
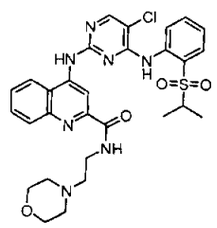
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
184	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-methylisoindolin-1-one	8.53(d, 1H); 8.32(s, 1H), 8.11(s, 1H); 7.81(dd, 1H); 7.73(dt, 1H); 7.33(t, 1H);7.28(s, 1H);4.72 (m,1H); 4.39 (s, 2H); 3.30 (m, 1H); 3.06(s, 3H); 1.28 (d, 6H), 1.15 (d, 6H). MS (ES^+): 530.2 $(M+1)^+$.
185	 8-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyrimidin-2-ylamino)-9-isopropoxy-3-methyl-1,2,3,4-tetrahydrobenzo[c][1,7]naphthyridin-6(5H)-one	MS (ES^+): 597.1 $(M+1)^+$.
186	 (S)-6-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyrimidin-2-ylamino)-2-(1-(2-hydroxyethyl)piperidin-3-yl)-5-isopropoxyisoindolin-1-one	MS (ES^+): 643.2 $(M+1)^+$.
187	 (R)-6-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyrimidin-2-ylamino)-2-(1-(2-hydroxyethyl)piperidin-3-yl)-5-isopropoxyisoindolin-1-one	MS (ES^+): 643.2 $(M+1)^+$.

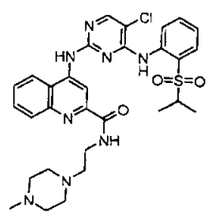
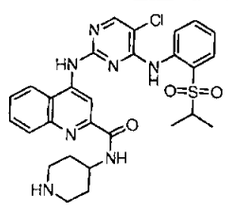
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
188	 6-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyrimidin-2-ylamino)-5-isopropoxy-2-(1,2,2,6,6-pentamethylpiperidin-4-yl)isoindolin-1-one	MS (ES^+): 669.3 $(M+1)^+$.
189	 (2S,4S)-4-(6-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino)pyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)-1-methylpyrrolidine-2-carboxamide	MS (ES^+): 642.2 $(M+1)^+$.
190	 5-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyrimidin-2-ylamino)-2-(1-(2-hydroxyethyl)piperidin-4-yl)-6-isopropoxyisoindoline-1,3-dione	MS (ES^+): 657.2 $(M+1)^+$.

	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
191	 2-(4-(5-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyrimidin-2-ylamino)-6-isopropoxy-1,3-dioxoisoindolin-2-yl)piperidin-1-yl)acetamide	MS (ES$^+$): 670.2 (M+1)$^+$.
192	 3-(4-(5-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino)pyrimidin-2-ylamino)-6-isopropoxy-1,3-dioxoisoindolin-2-yl)piperidin-1-yl)propanenitrile	MS (ES$^+$): 666 (M+1)$^+$.
193	 (S)-5-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyrimidin-2-ylamino)-6-isopropoxy-2-(1-methylpyrrolidin-3-yl)isoindoline-1,3-dione	MS (ES$^+$): 613.1 (M+1)$^+$.

120

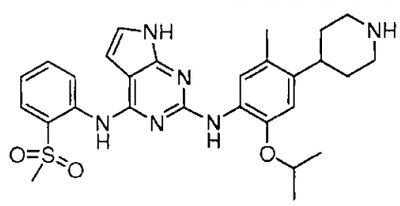
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
194	 (S)-5-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyrimidin-2-ylamino)-2-(1-(2-hydroxyethyl)pyrrolidin-3-yl)-6-isopropoxyisoindoline-1,3-dione	MS (ES^+): 643.1 $(M+1)^+$.
195	 (S)-5-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyrimidin-2-ylamino)-6-isopropoxy-2-(1-methylpyrrolidin-3-yl)isoindoline-1,3-dione	MS (ES^+): 613.1 $(M+1)^+$.
196	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-(1-methylpiperidin-4-yl)isoindolin-1-one	8.44(s,2H);8.39(s.1H);7.87(dd,1H);7.78(dt,1H);7.45(s,1H);7.41(m,1H);4.91(m,2H); 4.25(m,2H); 3.51 (m,3H); 3.10 (m,2H); 2.77 (s,3H); 1.80(m,2H),1.35(d,6H);1.13(d,6H). MS (ES^+): 614.2 $(M+1)^+$.

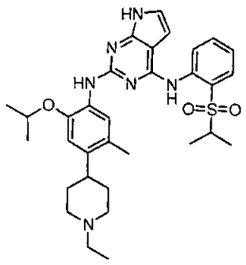
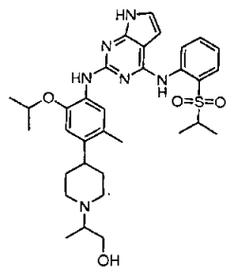
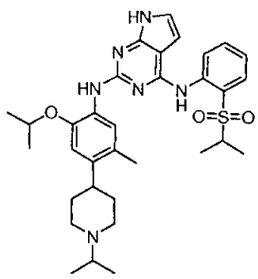
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
197	 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-((6S,7R)-9-methyl-9-aza-bicyclo[4.2.1]nonan-7-yl)isoindolin-1-one	MS (ES^+): 654.2 $(M+1)^+$.
198	 4-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-6-methyl-quinoline-2-carboxylic acid amide	^{1}H NMR (DMSO, 400 MHz) δ 10.04 (s, 1H), 9.66 (s, 1H), 8.47-8.63 (m, 3H), 8.18-8.23 (m, 2H), 7.97-7.99 (d, 1H), 7.54-7.82 (m, 3H), 7.25-7.35 (m, 1H), 3.31-3.33 (m, 1H), 2.54 (s, 3H), 1.15 (d, 6H). MS (ES^+): 511.1 $(M+1)^+$.
199	 4-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-6-methyl-quinoline-2-carboxylic acid methylamide	^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.73 (s, 1H), 8.85 (s, 1H), 8.21-8.55 (m, 1H), 8.21 (s, 1H), 8.08-8.18 (m, 1H), 7.90-7.92 (d, 1H), 7.81-7.83 (dd, 1H), 7.51-7.67 (m, 4H), 7.18-7.21 (m, 1H), 3.13-3.16 (m, 1H), 3.03-3.05 (d, 3H), 1.23-1.25 (d, 3H). MS (ES^+): 525.7 $(M+1)^+$.
200	 4-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-quinoline-2-carboxylic acid (2-morpholin-4-yl-ethyl)-amide	^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.79 (s, 1H), 9.00 (s, 1H), 8.57-8.59 (m, 2H), 8.30 (s, 1H), 8.11-8.13 (d, 1H), 7.99-8.01 (d, 1H), 7.88-7.91 (dd, 1H), 7.20-7.78 (m, 4H), 7.24-7.26 (m, 1H), 3.78-3.80 (m, 4H), 3.64-3.69 (m, 2H), 3.20-3.23 (m, 1H), 2.67-2.71 (m, 2H), 2.58-2.60 (m, 2H), 1.25-1.31 (d, 3H). MS (ES^+): 610.7 $(M+1)^+$.

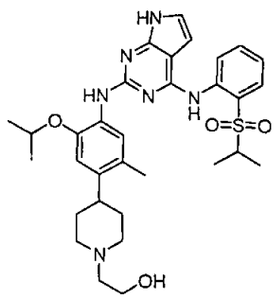
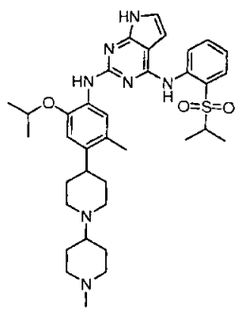
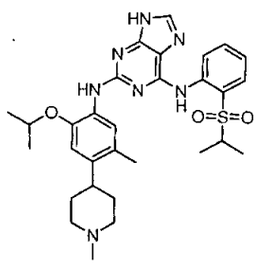
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
201	 4-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-quinoline-2-carboxylic acid [2-(4-methyl-piperazin-1-yl)-ethyl]-amide	^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.73 (s, 1H), 8.93 (s, 1H), 8.43-8.52 (m, 2H), 8.22 (s, 1H), 8.03-8.05 (d, 1H), 7.93-7.95 (d, 1H), 7.82-7.84 (dd, 1H), 7.54-7.72 (m, 4H), 7.16-7.20 (m, 1H), 4.43-4.48 (m, 8H), 3.58-3.62 (m, 2H), 3.11-3.18 (m, 1H), 2.67-2.71 (m, 2H), 2.46 (s, 3H), 1.23-1.25 (d, 6H). MS (ES^+): 623.8 $(M+1)^+$.
202	 4-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-quinoline-2-carboxylic acid piperidin-4-ylamide	^{1}H NMR (CD_3OD, 400 MHz) δ 8.92 (s, 1H), 8.68-8.70 (d, 1H), 8.46-8.48 (m, 2H), 8.26-8.28 (d, 1H), 7.96-7.99 (m, 2H), 7.79-7.83 (t, 1H), 7.67-7.71 (t, 1H), 7.38-7.42 (t, 1H), 4.31-4.33 (m, 1H), 3.60-3.63 (m, 2H), 3.40-3.46 (m, 1H), 3.27-3.33 (m, 2H), 2.33-2.37 (m, 2H), 2.05-2.08 (m, 2H), 1.35-1.37 (d, 6H). MS (ES^+): 580.7 $(M+1)^+$.

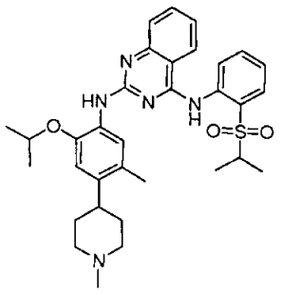
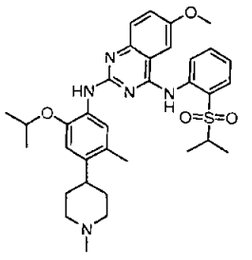
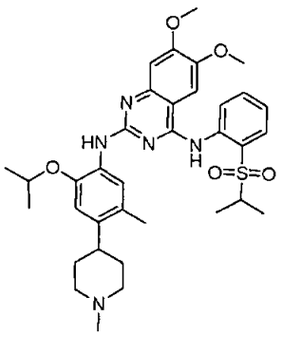
[0137] Table 2 shows exemplary compounds of Formula (1C).

Table 2

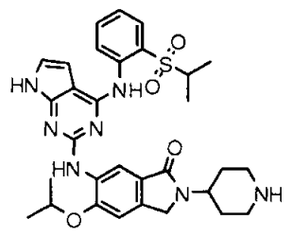
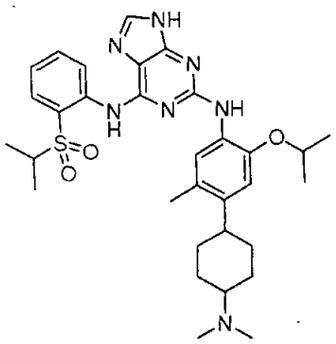
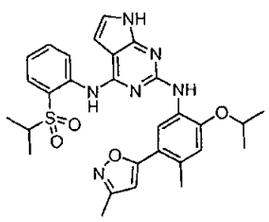
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
203	 N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(methylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine	MS (ES^+): 534.6 $(M+1)^+$

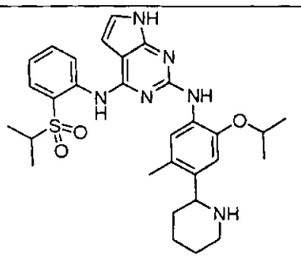
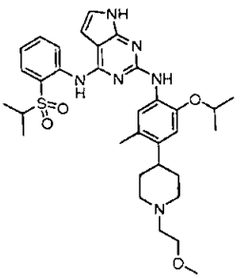
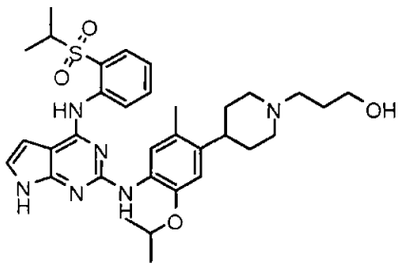
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
204	 N2-(4-(1-ethylpiperidin-4-yl)-2-isopropoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine	MS (ES^+): 590.8 $(M+1)^+$.
205	 2-(4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)piperidin-1-yl)propan-1-ol	MS (ES^+): 620.3 $(M+1)^+$.
206	 N2-(2-isopropoxy-4-(1-isopropylpiperidin-4-yl)-5-methylphenyl)-N4-(2-(isopropylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine	MS (ES^+): 604.8 $(M+1)^+$.

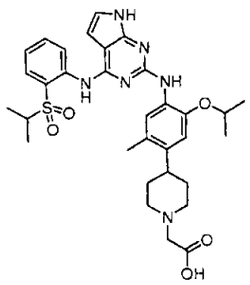
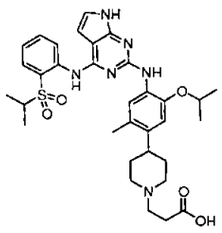
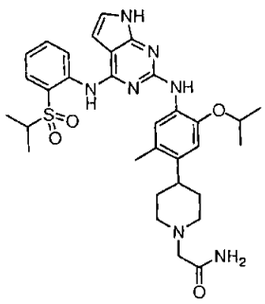
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
207	 2-(4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)piperidin-1-yl)ethanol	MS (ES^+): 606.8 $(M+1)^+$.
208	 N2-(2-isopropoxy-5-methyl-4-(1'-methyl-1,4'-bipiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)-7H-pyrrolo[2.3-d]pyrimidine-2,4-diamine	MS (ES^+): 659.8 $(M+1)^+$.
209	 N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N6-(2-(isopropylsulfonyl)phenyl)-9H-purine-2,6-diamine	MS (ES^+): 577.7 $(M+1)^+$.

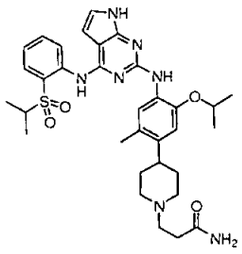
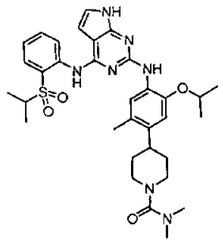
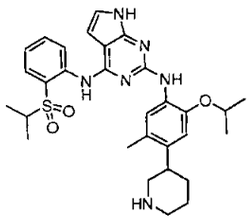
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
210	 N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)quinazoline-2,4-diamine	MS (ES$^+$): 588.7 $(M+1)^+$.
211	 N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-6-methoxyquinazoline-2,4-diamine	MS (ES$^+$): 618.8 $(M+1)^+$.
212	 N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-6,7-dimethoxyquinazoline-2,4-diamine	MS (ES$^+$): 648.8 $(M+1)^+$.

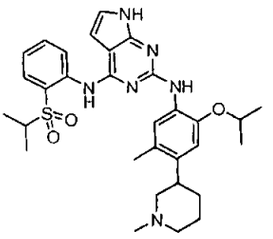
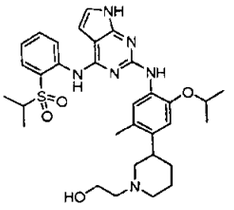
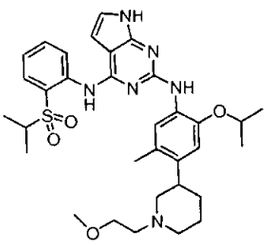
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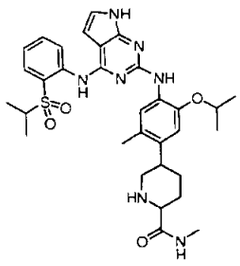
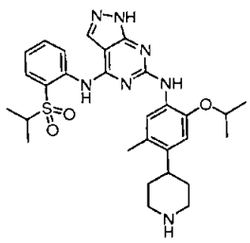
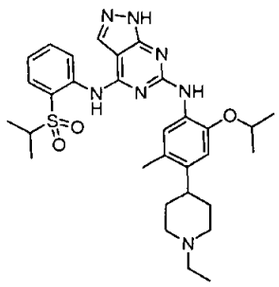
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
213	 5-isopropoxy-6-(4-(2-(isopropylsulfonyl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-(piperidin-4-yl)isoindolin-1-one	MS (ES^+): 604.7 $(M+1)^+$.
214	 N2-(4-(4-(dimethylamino)cyclohexyl)-2-isopropoxy-5-methylphenyl)-N6-(2-(isopropylsulfonyl)phenyl)-9H-purine-2,6-diamine	MS (ES^+): 606.7 $(M+1)^+$.
215	 N2-(2-isopropoxy-4-methyl-5-(3-methylisoxazol-5-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine	MS (ES^+): 561.6 $(M+1)^+$.

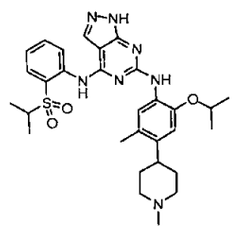
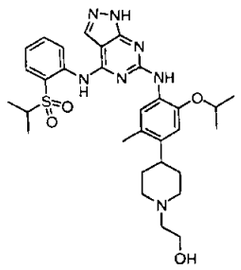
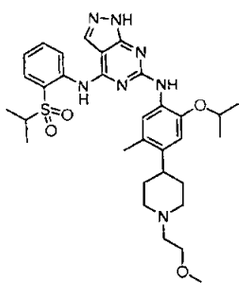
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
216	 N2-(2-isopropoxy-5-methyl-4-(piperidin-2-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine	MS (ES^+): 563.2 $(M+1)^+$.
217	 N2-(2-isopropoxy-4-(1-(2-methoxyethyl)piperidin-4-yl)-5-methylphenyl)-N4-(2-(isopropylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine	MS (ES^+): 621.8 $(M+1)^+$.
218	 3-(4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)piperidin-1-yl)propan-1-ol	MS (ES^+): 621.8 $(M+1)^+$.

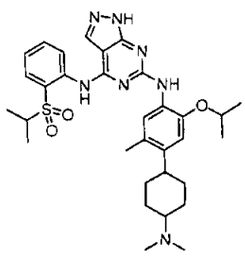
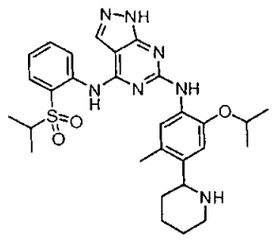
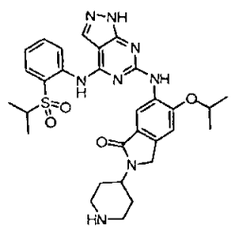
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
219	 2-(4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)piperidin-1-yl)acetic acid	MS (ES^+): 621.7 $(M+1)^+$.
220	 3-(4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)piperidin-1-yl)propanoic acid	MS (ES^+): 635.8 $(M+1)^+$.
221	 2-(4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)piperidin-1-yl)acetamide	MS (ES^+): 620.2 $(M+1)^+$.

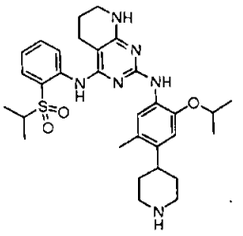
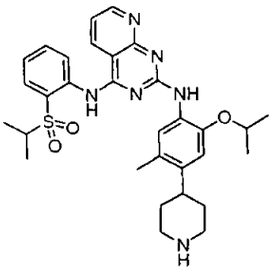
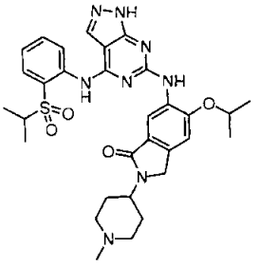
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
222	 3-(4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)piperidin-1-yl)propanamide	MS (ES^+): 634.8 $(M+1)^+$.
223	 4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)-N,N-dimethylpiperidine-1-carboxamide	MS (ES^+): 634.8 $(M+1)^+$.
224	 N2-(2-isopropoxy-5-methyl-4-(piperidin-3-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine	MS (ES^+): 563.7 $(M+1)^+$.

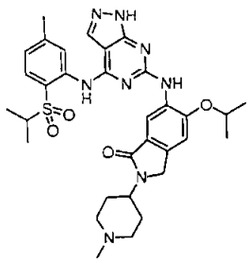
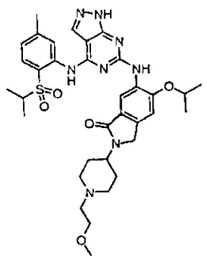
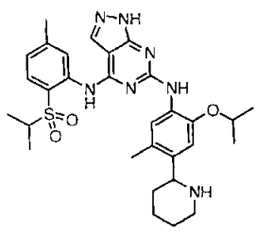
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
225	 N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-3-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine	MS (ES$^+$): 576.7 $(M+1)^+$.
226	 2-(3-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)piperidin-1-yl)ethanol	MS (ES$^+$): 607.8 $(M+1)^+$.
227	 N2-(2-isopropoxy-4-(1-(2-methoxyethyl)piperidin-3-yl)-5-methylphenyl)-N4-(2-(isopropylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine	MS (ES$^+$): 621.8 $(M+1)^+$.

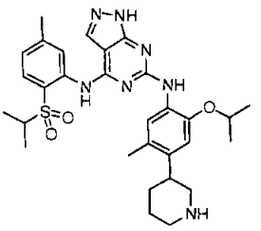
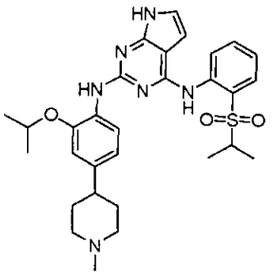
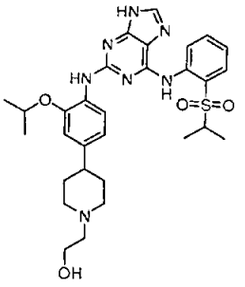
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
228	 5-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)-N-methylpiperidine-2-carboxamide	MS (ES$^+$): 620.7 (M+1)$^+$.
229	 N6-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine	MS (ES$^+$): 564.7 (M+1)$^+$.
230	 N6-(4-(1-ethylpiperidin-4-yl)-2-isopropoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine	MS (ES$^+$): 592.7 (M+1)$^+$.

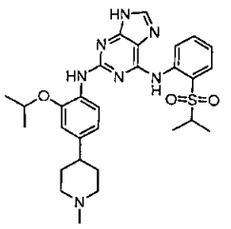
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
231	 N6-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine	MS (ES$^+$): 578.7 $(M+1)^+$.
232	 2-(4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methylphenyl)piperidin-1-yl)ethanol	MS (ES$^+$): 608.7 $(M+1)^+$.
233	 N6-(2-isopropoxy-4-(1-(2-methoxyethyl)piperidin-4-yl)-5-methylphenyl)-N4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine	MS (ES$^+$): 622.7 $(M+1)^+$.

	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
234	 N6-(4-(4-(dimethylamino)cyclohexyl)-2-isopropoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine	MS (ES^+): 606.8 $(M+1)^+$.
235	 N6-(2-isopropoxy-5-methyl-4-(piperidin-2-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine	MS (ES^+): 564.7 $(M+1)^+$.
236	 5-isopropoxy-6-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-(piperidin-4-yl)isoindolin-1-one	MS (ES^+): 605.7 $(M+1)^+$.

	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
237	 N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine-2,4-diamine	MS (ES^+): 579.7 $(M+1)^+$.
238	 N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrido[2,3-d]pyrimidine-2,4-diamine	MS (ES^+): 575.7 $(M+1)^+$.
239	 5-isopropoxy-6-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-(1-methylpiperidin-4-yl)isoindolin-1-one	MS (ES^+): 619.7 $(M+1)^+$.

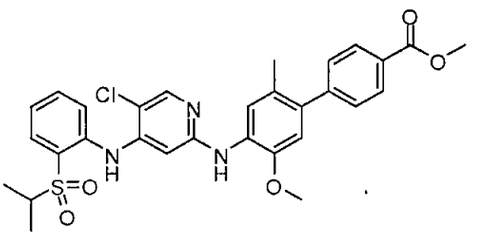
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
240	 5-isopropoxy-6-(4-(2-(isopropylsulfonyl)-5-methylphenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-(1-methylpiperidin-4-yl)isoindolin-1-one	MS (ES^+): 633.7 $(M+1)^+$.
241	 5-isopropoxy-6-(4-(2-(isopropylsulfonyl)-5-methylphenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-(1-(2-methoxyethyl)piperidin-4-yl)isoindolin-1-one	MS (ES^+): 677.8 $(M+1)^+$.
242	 N6-(2-isopropoxy-5-methyl-4-(piperidin-2-yl)phenyl)-N4-(2-(isopropylsulfonyl)-5-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine	MS (ES^+): 578.7 $(M+1)^+$.

	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
243	 N6-(2-isopropoxy-5-methyl-4-(piperidin-3-yl)phenyl)-N4-(2-(isopropylsulfonyl)-5-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine	MS (ES^+): 578.7 $(M+1)^+$.
244	 N2-(2-isopropoxy-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine	MS (ES^+): 562.3 $(M+1)^+$.
245	 2-(4-(3-isopropoxy-4-(6-(2-(isopropylsulfonyl) phenylamino)-9H-purin-2-ylamino)phenyl)piperidin-1-yl)ethanol	MS (ES^+): 593.7 $(M+1)^+$.

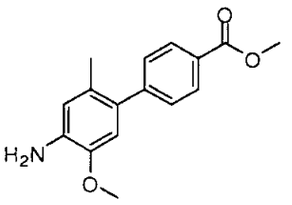
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
246	 N2-(2-isopropoxy-4-(1-methylpiperidin-4-yl)phenyl)-N6-(2-(isopropylsulfonyl)phenyl)-9H-purine-2,6-diamine	MS (ES^+): 563.7 $(M+1)^+$.

Example 17

Methyl 4'-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino)pyridin-2-ylamino)-5'-methoxy-2'-methylbiphenyl-4-carboxylate (**254**)

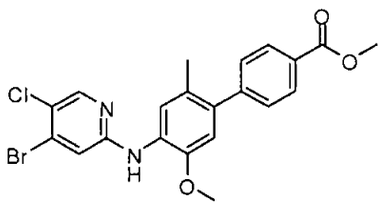


Step 1: Methyl 4'-amino-5'-methoxy-2'-methylbiphenyl-4-carboxylate



[0138] Methyl 4'-amino-5'-methoxy-2'-methylbiphenyl-4-carboxylate; MS m/z 272.1 (M+1), may be synthesized following the procedures previously described (**Example 7, Steps 1 and 2**) using appropriate reagents.

Step 2: Methyl 4'-(4-bromo-5-chloropyridin-2-ylamino)-5'-methoxy-2'-methylbiphenyl-4-carboxylate



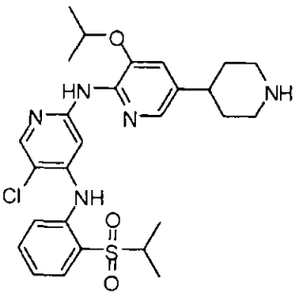
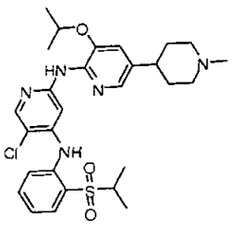
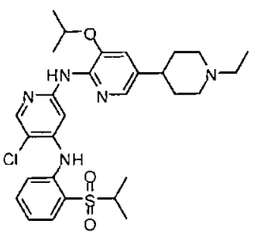
[0139] Methyl 4'-amino-5'-methoxy-2'-methylbiphenyl-4-carboxylate generated in Step 1 (200 mg, 0.75 mmol), 2,4-dibromo-5-chloropyridine (222 mg, 0.82 mmol, 1.1 equiv), $Pd_2(dba)_3$ (17 mg, 0.02 mmol, 0.025 equiv.), xantphos (22 mg, 0.04 mmol, 0.05 equiv.), and Cs_2CO_3 (365 mg, 1.1 mmol, 1.5 equiv.) are added to THF (5 mL). The resulting mixture is bubbled with N_2 gas for 5 minutes and then heated at 150 °C for 4 hours. After cooling to room temperature, the reaction mixture is diluted into EtOAc and washed with H_2O. The EtOAc layer is dried over Mg_2SO_4 and concentrated *in vacuo*. Silica gel chromatography (hexanes-EtOAc) affords Methyl 4'-(4-bromo-5-chloropyridin-2-ylamino)-5'-methoxy-2'-methylbiphenyl-4-carboxylate; MS m/z 461.0 (M+1).

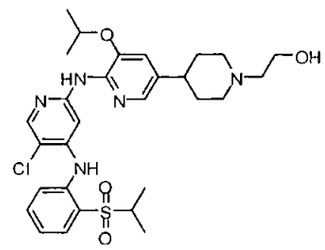
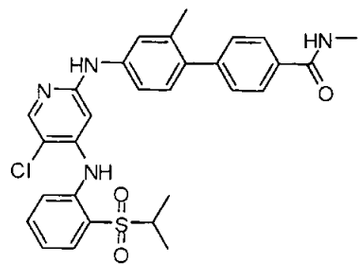
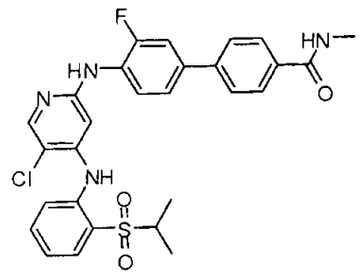
Step 3: Methyl 4'-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino)pyridin-2-ylamino)-5'-methoxy-2'-methylbiphenyl-4-carboxylate (254)

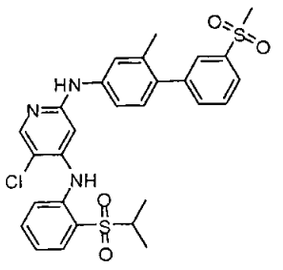
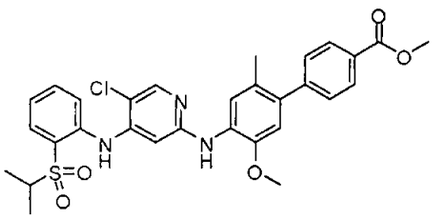
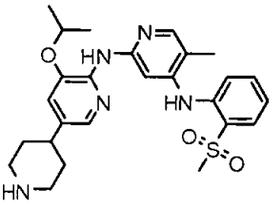
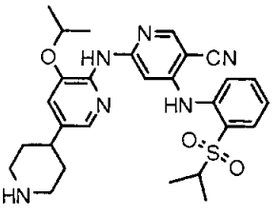
[0140] Methyl 4'-(4-bromo-5-chloropyridin-2-ylamino)-5'-methoxy-2'-methylbiphenyl-4-carboxylate generated in Step 2 (9 mg, 0.022 mmol), 2-(isopropylsulfonyl)aniline (4 mg, 0.022 mmol, 1 equiv), $Pd_2(dba)_3$ (1.7 mg, 0.002 mmol, 0.1 equiv.), 2-(Dicyclohexylphosphino)-2',4',6'-tri-i-propyl-1,1'-biphenyl (1.8 mg, 0.004 mmol, 0.2 equiv.), and Sodium tert-butoxide (2.7 mg, 0.028 mmol, 1.3 equiv.) are added to THF (1 mL). The resulting mixture is bubbled with N_2 gas for 5 minutes and then heated at 150 °C for 4 hours. After cooling to room temperature, the reaction mixture is diluted into EtOAc and washed with H_2O. The EtOAc layer is dried over Mg_2SO_4 and concentrated *in vacuo*. Silica gel chromatography (hexanes-EtOAc) affords Methyl 4'-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino)pyridin-2-ylamino)-5'-methoxy-2'-methylbiphenyl-4-carboxylate (**254**); MS m/z 580.2 (M+1).

[0141] Exemplary compounds of the invention are set forth below. Table 3 shows exemplary compounds of Formula (5).

Table 3

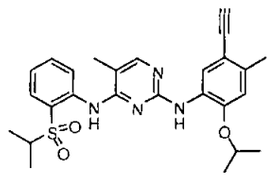
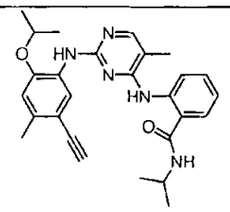
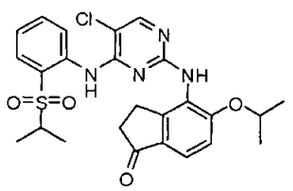
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
247	 5-chloro-N2-(3-isopropoxy-5-(piperidin-4-yl)pyridin-2-yl)-N4-(2-(isopropylsulfonyl)phenyl)pyridine-2,4-diamine	MS (ES$^+$): 544.2 $(M+1)^+$.
248	 5-chloro-N2-(3-isopropoxy-5-(1-methylpiperidin-4-yl)pyridin-2-yl)-N4-(2-(isopropylsulfonyl) phenyl)pyridine-2,4-diamine	MS (ES$^+$): 558.2 $(M+1)^+$.
249	 5-chloro-N2-(5-(1-ethylpiperidin-4-yl)-3-isopropoxypyridin-2-yl)-N4-(2-(isopropylsulfonyl) phenyl)pyridine-2,4-diamine	MS (ES$^+$): 572.2 $(M+1)^+$.

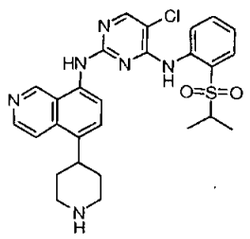
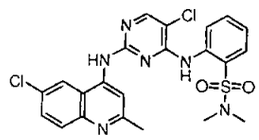
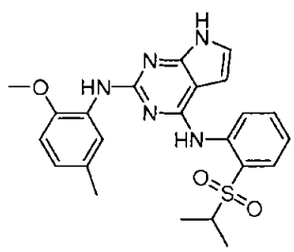
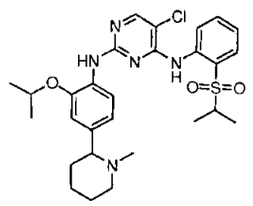
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
250	 2-(4-(6-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino)pyridin-2-ylamino)-5-isopropoxypyridin-3-yl)piperidin-1-yl)ethanol	MS (ES^+): 588.2 $(M+1)^+$.
251	 4'-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyridin-2-ylamino)-N,2'-dimethylbiphenyl-4-carboxamide	MS (ES^+): 549.2 $(M+1)^+$.
252	 4'-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyridin-2-ylamino)-3'-fluoro-N-methylbiphenyl-4-carboxamide	MS (ES^+): 553.1 $(M+1)^+$.

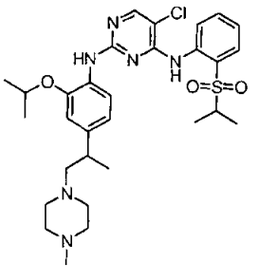
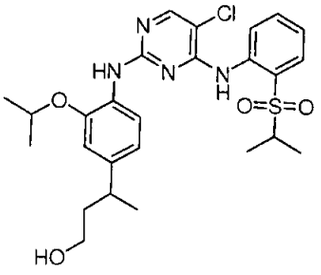
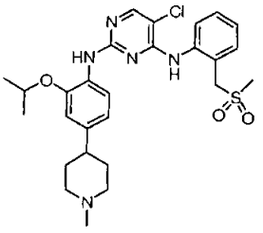
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
253	 5-chloro-N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methyl-3'-(methylsulfonyl)biphenyl-4-yl)pyridine-2,4-diamine	MS (ES^+): 570.1 $(M+1)^+$.
254	 Methyl 4'-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino)pyridin-2-ylamino)-5'-methoxy-2'-methylbiphenyl-4-carboxylate	MS m/z 580.2 $(M+1)^+$.
255	 N2-(3-isopropoxy-5-(piperidin-4-yl)pyridin-2-yl)-5-methyl-N4-(2-(methylsulfonyl)phenyl)pyridine-2,4-diamine	MS (ES^+): 495.6 $(M+1)^+$.
256	 6-(3-isopropoxy-5-(piperidin-4-yl)pyridin-2-ylamino)-4-(2-(isopropylsulfonyl)phenylamino) nicotinonitrile	MS (ES^+): 534.6 $(M+1)^+$.

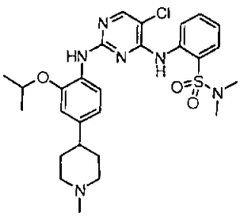
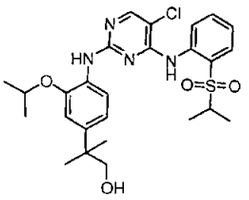
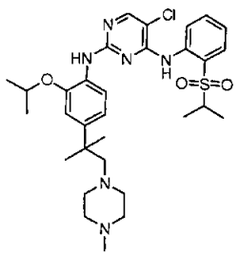
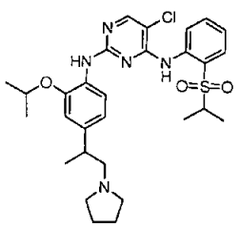
[0142] Table 4 shows other compounds which may be useful treating, ameliorating or preventing a condition which responds to inhibition of anaplastic lymphoma kinase (ALK) activity, focal adhesion kinase (FAK), zeta-chain-associated protein kinase 70 (ZAP-70), insulin-like growth factor (IGF-1R).

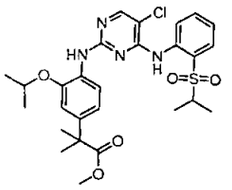
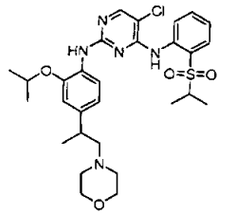
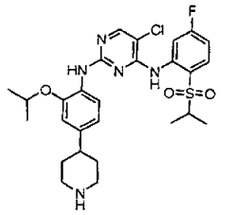
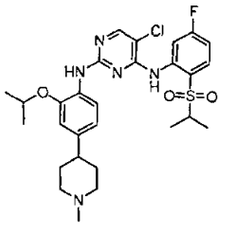
Table 4

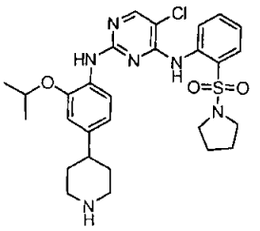
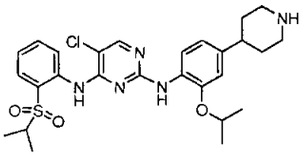
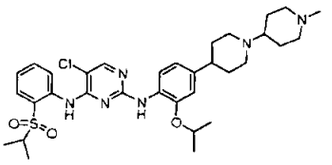
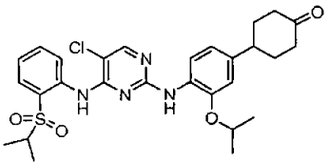
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
257	 N2-(5-Ethynyl-2-isopropoxy-4-methyl-phenyl)-5-methyl-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine	MS (ES$^+$): 479.2 (M+1)$^+$.
258	 2-(2-(5-ethynyl-2-isopropoxy-4-methylphenylamino)-5-methylpyrimidin-4-ylamino)-N-isopropylbenzamide	MS (ES$^+$): 458.6 (M+1)$^+$.
259	 4-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2,3-dihydro-5-isopropoxyinden-1-one	MS (ES$^+$): 515.1 (M+1)$^+$.

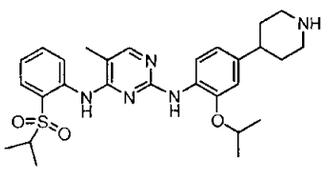
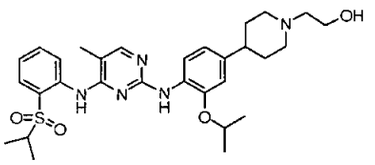
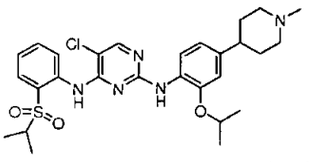
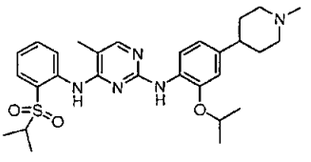
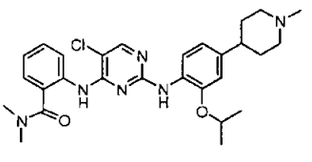
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
260	 5-chloro-N4-(2-(isopropylsulfonyl)phenyl)-N2-(5-(piperidin-4-yl)isoquinolin-8-yl)pyrimidine-2,4-diamine	MS (ES$^+$): 537.1 (M+1)$^+$.
261	 2-[5-Chloro-2-(6-chloro-2-methyl-quinolin-4-ylamino)-pyrimidin-4-ylamino]-N,N-dimethyl-benzenesulfonamide	^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.45 (s, 1H), 8.34-8.37 (d, 1H), 8.20 (s, 1H), 8.10 (s, 1H), 7.82-7.9 (m, 3H), 7.52-7.60 (m. 3H), 7.19-7.26 (m, 1H), 2.69 (s. 6H), 2.54 (s, 3H). MS (ES$^+$): 503.0 (M+1)$^+$.
262	 N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methoxy-5-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine	MS (ES$^+$): 451.5 (M+1)$^+$.
263	 5-chloro-N2-(2-isopropoxy-4-(1-methylpiperidin-2-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES$^+$): 558.1 (M+1)$^+$.

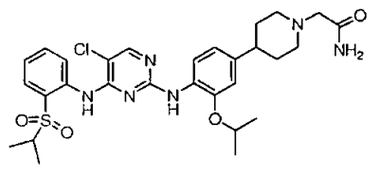
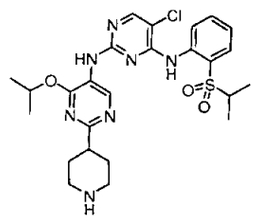
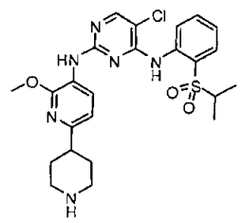
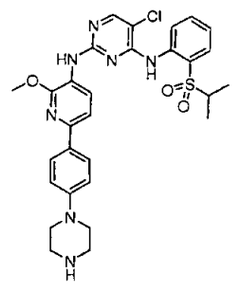
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
264	 5-chloro-N2-(2-isopropoxy-4-(1-(4-methylpiperazin-1-yl)propan-2-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine	MS (ES^+): 601.2 $(M+1)^+$.
265	 3-(4-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyrimidin-2-ylamino)-3-isopropoxyphenyl)butan-1-ol	MS (ES^+): 533.1 $(M+1)^+$.
266	 5-chloro-N2-(2-isopropoxy-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(methylsulfonylmethyl) phenyl)pyrimidine-2,4-diamine	MS (ES^+): 544.1 $(M+1)^+$.

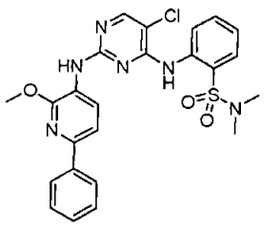
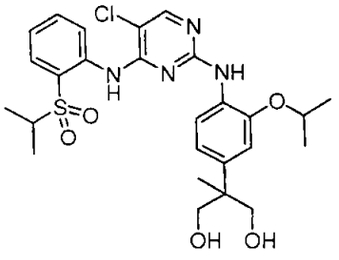
	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
267	 2-(5-chloro-2-(2-isopropoxy-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide	MS (ES^+): 559.1 $(M+1)^+$.
268	 2-(4-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyrimidin-2-ylamino)-3-isopropoxyphenyl)-2-methylpropan-1-ol	MS (ES^+): 533.1 $(M+1)^+$.
269	 5-chloro-N2-(2-isopropoxy-4-(2-methyl-1-(4-methylpiperazin-1-yl)propan-2-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 615.3 $(M+1)^+$.
270	 5-chloro-N2-(2-isopropoxy-4-(1-(pyrrolidin-1-yl)propan-2-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine	MS (ES^+): 572.2 $(M+1)^+$.

	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
271	 Methyl 2-(4-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino)pyrimidin-2-ylamino)-3-isopropoxyphenyl)-2-methylpropanoate	MS (ES^+): 561.1 $(M+1)^+$.
272	 5-chloro-N2-(2-isopropoxy-4-(1-morpholinopropan-2-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 588.2 $(M+1)^+$.
273	 5-chloro-N4-(5-fluoro-2-(isopropylsulfonyl)phenyl)-N2-(2-isopropoxy-4-(piperidin-4-yl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 562.1 $(M+1)^+$.
274	 5-chloro-N4-(5-fluoro-2-(isopropylsulfonyl)phenyl)-N2-(2-isopropoxy-4-(1-methylpiperidin-4-yl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 576.2 $(M+1)^+$.

	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
275	 5-chloro-N2-(2-isopropoxy-4-(piperidin-4-yl)phenyl)-N4-(2-(pyrrolidin-1-ylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 571.1 $(M+1)^+$.
276	 5-chloro-N2-(2-isopropoxy-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 544.1 $(M+1)^+$.
277	 5-chloro-N2-(2-isopropoxy-4-(1-(1-methylpiperidin-4-yl)piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 641.3 $(M+1)^+$.
278	 4-(4-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-3-isopropoxyphenyl)cyclohexanone	MS (ES^+): 557.1 $(M+1)^+$.

	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
279	 N2-(2-isopropoxy-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine	MS (ES^+): 524.2 $(M+1)^+$.
280	 2-(4-(4-(4-(2-(isopropylsulfonyl)phenylamino)-5-methylpyrimidin-2-ylamino)-3-isopropoxy phenyl)piperidin-1-yl)ethanol	MS (ES^+): 568.7 $(M+1)^+$.
281	 5-chloro-N2-(2-isopropoxy-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine	MS (ES^+): 558.1 $(M+1)^+$.
282	 N2-(2-isopropoxy-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine	MS (ES^+): 538.7$(M+1)^+$.
283	 2-(2-(2-isopropoxy-4-(1-methylpiperidin-4-yl)phenylamino)-5-chloropyrimidin-4-ylamino)-N,N-dimethylbenzamide	MS (ES^+): 523.0 $(M+1)^+$.

	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
284	 2-(4-(4-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-3-isopropoxyphenyl) piperidin-1-yl)acetamide	MS (ES^+): 601.1 $(M+1)^+$.
285	 5-chloro-N2-(4-isopropoxy-2-(piperidin-4-yl)pyrimidin-5-yl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine	MS (ES^+): 546.1 $(M+1)^+$.
286	 5-chloro-N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methoxy-6-(piperidin-4-yl)pyridin-3-yl) pyrimidine-2,4-diamine	MS (ES^+): 517.1 $(M+1)^+$.
287	 5-chloro-N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methoxy-6-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)pyrimidine-2,4-diamine	MS (ES^+): 594.1 $(M+1)^+$.

	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d6) and/or MS (m/z)
288	 2-(5-chloro-2-(2-methoxy-6-phenylpyridin-3-ylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide	MS (ES$^+$): 511.1 $(M+1)^+$.
289	 2-(4-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyrimidin-2-ylamino)-3-isopropoxyphenyl)-2-methylpropane-1,3-diol	MS (ES$^+$): 548.1 $(M+1)^+$.

[0143] Compounds of the present invention may be assessed for their ability to inhibit ALK using assays described below, as well as other assays known in the art.

Ba/F3 cell line panel and reagents

[0144] Ba/F3 is a murine IL-3-dependent pro-B lymphoma cell line. Parental Ba/F3 cells are used to generate a panel of sublines whose proliferation and survival is rendered IL-3-independent by stable transduction with individual tyrosine kinases activated by fusion with the amino-terminal portion of TEL (amino acid 1-375) or BCR. In order to generate Ba/F3 cell lines transformed by Tel-Tyrosine Kinase (TK) fusions, parental Ba/F3 cells are infected with a retrovirus harboring each kinase domain and subjected to puromycin selection and IL-3 withdrawal to obtain IL-3-independent, transformed Ba/F3 cells.

[0145] Each transformed Ba/F3 cells are cultured in RPMI-1640 media (Gibco Cat #11875093, Carlsbad, CA) supplemented with 10% FBS (Hyclone Cat #SV30014.03, Logan,

UT). 4.5 g/L glucose (Sigma #G5400, St.Louis, MO), 1.5 g/L sodium bicarbonate (Biowhittaker #17-613E, Walkersville, MD) and Pen/Strep (Gibco #10378-016, Carlsbad, CA). Cells are splitted twice weekly.

Ba/F3 cell viability inhibition assay

[0146] The potency of test compounds against various Tel-TK transformed Ba/F3 lines is determined as follows. Exponentially growing BaF3 Tel-TK cells are diluted in fresh medium to 75,000 cells/mL and seeded into 384-well plates (3750 cells/well) at 50 µL/well using a µFill liquid dispenser (BioTek, Winooski, VT, USA). Duplicate plates are run for each cell line. Test and control compounds are serially diluted with DMSO and arrayed in a polypropylene 384-well plate. 50 nL of compound is transferred into the assay plates using a pin-transfer device, and the plates are incubated at 37 °C (5% CO2) for 48 hours. 25 µL Bright-Glo (Promega, Madison, WI, USA) is added and luminescence is quantified using Analyst GT (Perkin Elmer, Wellesley, MA). Custom curve-fitting software is used to produce a logistic fit of percent cell viability as a function of the logarithm of inhibitor concentration. The IC_{50} is interpolated as the concentration of compound needed to reduce cell viability to 50% of a DMSO control. Parental Ba/F3 cells that are maintained and cultured in presence of IL-3 (1 ng/ml in final) are diluted in fresh medium containing IL-3 (1 ng/ml in final) to 75,000 cells/mL following the same procedure as described above.

Kapas 299 cellular assay

[0147] Luciferized Karpas 299 (Karpas299-Luc) is generated by infecting retrovirus encoding luciferase gene, and cultured in RPMI-1649 medium supplemented with 10% FBS, 1% P/S/L-Glu. At day 1, cells are harvested and resuspended at density of 150,000 cells/ml (cell number is measured using ViCell (BD). Cells are dispensed from a diluted suspension into a 384-well assay plate in 50 µl volume using µFill (Bio-TEK). Serially diluted compounds (in DMSO) are transferred into plate using 50 nL pinhead. Assay plates are incubated at 37 °C for 48 hours. At day 4, 25 µl/well of Bright-Glo reagent (Promega) is added using µFill (Bio-TEK). Within 30 minutes, a luciferase signal is measured using Analyst GT in default setting for luminescence detection.

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Enzymatic HTRF assay

[0148] ALK enzyme and IGF1R and INSR are purchased from Upstate. Following reagents are prepared in-house; 10 x kinas buffer (KB) (200 mM Tris (pH 7.0), 100 mM $MgCl_2$, 30 mM $MnCl_2$, 50 nM $NaVO_4$), 10 mM ATP, 100 mg/ml BSA, 0.5 M EDTA, 4 M KF. Proxiplate-384 from Perkin-Elmer is used for set up assay. All the HTRF reagents including substrate (Biotin-poly-GT (61GT0BLB), Mab PT66-K, (61T66KLB), Streptavidin-XL^{ent} (611SAXLB)) are purchased from CIS-US, Inc.

[0149] The substrate/ATP mix is prepared by adding ATP (final concentration, 3 μM) and biotinylated poly-GT (final concentration, 10 ng/μl) into 1x KB, and dispensed into Proxiplate-384 at 5 μl/well using μFill (Bio-TEK). Serially diluted compounds (in DMSO) are transferred into plate using 50 nL pinhead. 5 μL of prepared Enzyme mix (enzyme (final concentration, 5 ng/μl), mixed with BSA and DTT in 1x KB) is added to initiate kinase reaction using μFill (Bio-TEK). Assay plate is incubated at room temperature for 2 hours. Detection mix is prepared by adding both Mab PT66-K and Streptavidin-XL^{ent} into 0.5 x KB solution containing KF (final concentration, 125 mM), EDTA (final concentration, 50 mM) and BSA (final concentration, 100 μg/ml) in. At the end of reaction, 10 μL of detection mix is added and incubated for 30 minutes at room temperature before measurement. HTRF signal is detected using Analyst-GT (molecular dynamic).

Reporter assay in U2OS cells using RE1-pGL3 for IGF1-S3-5 or INSR-S3-5

[0150] Seed 10M cells / T175 Flask in Mc Coy 10% FBS and 4 days later, suck off media and add fresh media. Next day (5 days after seeding), trypsinize cells, wash once with PBS, then resuspend cells in Mc-Coy media 4% delipidated serum with P/S/G. Count cells and dilute to 400,000 cells/ml.

[0151] For 95 ml of cells (400000 cells/ml (40M)), prepare the following DNA/Fugene6 mix: 5 ml Mc-Coy media without serum; 120 μg DNA mix (20 μg IGF1R-S3-5 or INSR-S3-5+100 μg RE1-pGL3); and 240 μL Fugene6 reagent. Incubate DNA/ Fugene6 mix for 15 min before adding it to cells in 4% delipidated serum. Dispense 50 μL / well in 384 well plate. 22-24h later, add 50 nL of serially diluted compounds using pinhead. 30 min later, add 2 μL of 26X IGF1 (or 100X Insulin) dose diluted in Mc-Coy 4% delipidated serum using μ-Fill. 30 hours later, add 25 μL 100% bright-glo and read on Analyst-GT for measuring luminescence.

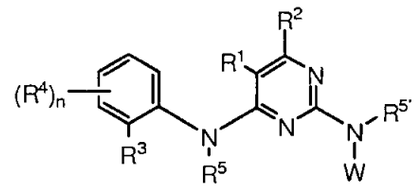
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[0152] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the 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.

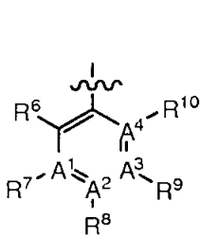
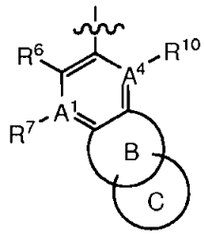
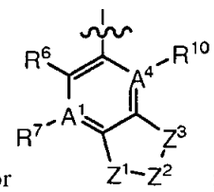
Claims

1. A compound having Formula (1):



(1)

or pharmaceutically acceptable salts thereof; wherein

W is  ,  or  ;

A^1 and A^4 are independently C or N;

each A^2 and A^3 is C, or one of A^2 and A^3 is N when R^6 and R^7 form a ring;

B and C are independently an optionally substituted 5-7 membered carbocyclic ring, aryl, heteroaryl or heterocyclic ring containing N, O or S;

Z^1, Z^2 and Z^3 are independently NR^{11}, C=O, CR-OR, $(CR_2)_{1-2}$ or =C-R^{12};

R^1 and R^2 are independently halo, OR^{12}, $NR(R^{12})$, SR^{12}, or an optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; or one of R^1 and R^2 is H;

R^3 is $(CR_2)_{0-2}SO_2R^{12}$, $(CR_2)_{0-2}SO_2NRR^{12}$, $(CR_2)_{0-2}CO_{1-2}R^{12}$, $(CR_2)_{0-2}CONRR^{12}$ or cyano;

R^4, R^6, R^7 and R^{10} are independently an optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; OR^{12}, $NR(R^{12})$, halo, nitro, SO_2R^{12}, $(CR_2)_pR^{13}$ or X; or R^4, R^7 and R^{10} are independently H;

R, R^5 and $R^{5'}$ are independently H or C_{1-6} alkyl;

R^8 and R^9 are independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo or X, or one of R^8 and R^9 is H when R^1 and R^2 form a ring; and provided one of R^8 and R^9 is X;

alternatively, R^1 and R^2, or R^6 and R^7, R^7 and R^8, or R^9 and R^{10}, when attached to a carbon atom may form an optionally substituted 5-7 membered monocyclic or fused carbocyclic ring, aryl, or heteroaryl or heterocyclic ring comprising N, O and/or S; or R^7, R^8, R^9 and R^{10} are absent when attached to N;

R^{11} is H, C_{1-6} alkyl, C_{2-6} alkenyl, $(CR_2)_pCO_{1-2}R$, $(CR_2)_pOR$, $(CR_2)_pR^{13}$, $(CR_2)_pNRR^{12}$, $(CR_2)_pCONRR^{12}$ or $(CR_2)_pSO_{1-2}R^{12}$;

R^{12} and R^{13} are independently an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, or a 5-7 membered heterocyclic ring comprising N, O and/or S; aryl or heteroaryl; or R^{12} is H, C_{1-6} alkyl;

X is $(CR_2)_qY$, cyano, $CO_{1-2}R^{12}$, $CONR(R^{12})$, $CONR(CR_2)_pNR(R^{12})$, $CONR(CR_2)_pOR^{12}$, $CONR(CR_2)_pSR^{12}$, $CONR(CR_2)_pS(O)_{1-2}R^{12}$ or $(CR_2)_{1-6}NR(CR_2)_pOR^{12}$;

Y is an optionally substituted 3-12 membered carbocyclic ring, a 5-12 membered aryl, or a 5-12 membered heteroaryl or heterocyclic ring comprising N, O and/or S and attached to A^2 or A^3 or both via a carbon atom of said heteroaryl or heterocyclic ring when q in $(CR_2)_qY$ is 0; and

n, p and q are independently 0-4.

2. The compound of claim 1,wherein R^1 is halo or C_{1-6} alkyl;

R^2 is H or NH_2; or

R^1 and R^2 together form an optionally substituted 5-6 membered aryl, or heteroaryl or heterocyclic ring comprising 1-3 nitrogen atoms.

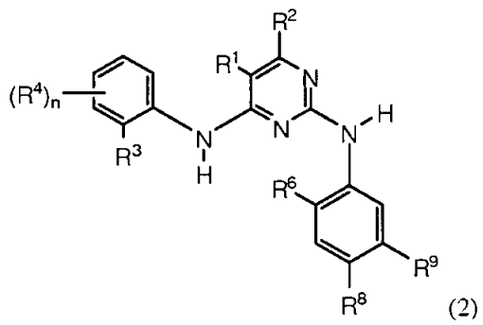
3. The compound of claim 1 or claim 2, wherein R^3 is SO_2R^{12}, SO_2NH_2, SO_2NRR^{12}, CO_2NH_2, $CONRR^{12}$, $CO_{1-2}R^{12}$, or cyano; and

R^{12} is C_{1-6} alkyl, an optionally substituted C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl or azetidinyl.

4. The compound of any one of claims 1-3, wherein R^5, $R^{5'}$, R^7 and R^{10} are independently H, and n is 0.

5. The compound of any one of claims 1-3, wherein R^6 is OR^{12}, and R^{12} is C_{1-6} alkyl.

6. The compound of any one of claims 1-3, wherein said compound is of Formula (2):



(2)

wherein R^1 is halo or C_{1-6} alkyl;

R^2 is H; or

R^1 and R^2 together form an optionally substituted 5-6 membered heteroaryl or heterocyclic ring comprising one or two nitrogen atoms;

R^6 is isopropoxy or methoxy;

one of R^8 and R^9 is $(CR_2)_qY$ and the other is C_{1-6} alkyl, cyano, $CO_{1-2}R^{12}$, $CONR(R^{12})$ or $CONR(CR_2)_pNR(R^{12})$;

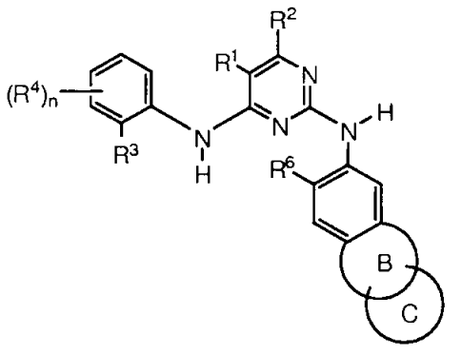
Y is an optionally substituted C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, or phenyl; or Y is pyridyl, pyrazolyl, isoxazolyl, imidazolyl, thiazolyl, benzimidazolyl, pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, azetidinyl, heptamethyleneimine or octamethyleneimine, each of which is attached to the phenyl ring via a carbon atom when q in $(CR_2)_qY$ is 0;

n is 0-1; and

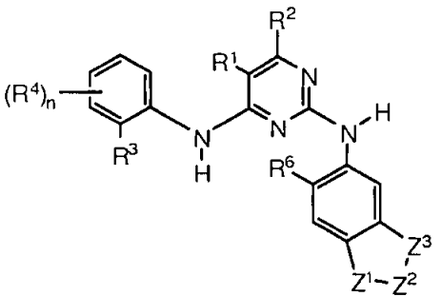
q is 0-4.

7. The compound of claim 6, wherein one of R^8 and R^9 is $(CR_2)_qY$ and the other is C_{1-6} alkyl; and n and q are independently 0.

8. The compound of claim 1, wherein said compound is of Formula (3A) or (3B):

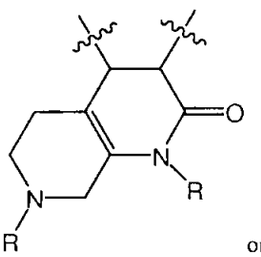


(3A)

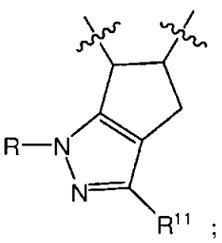


(3B)

wherein B and C together form

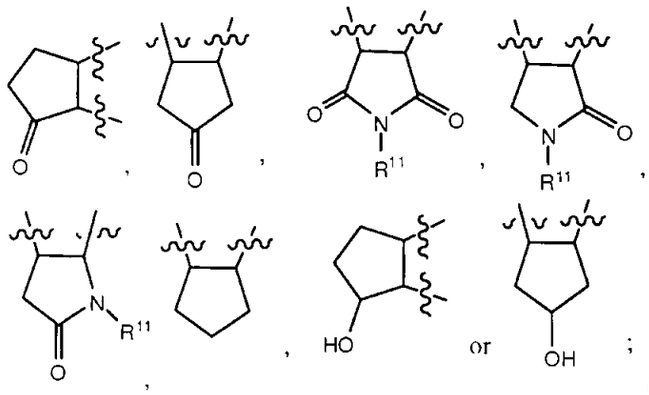


or



;

Z^1, Z^2 and Z^3 together form



or tautomers thereof;

R^1 is halo or C_{1-6} alkyl;

R^2 is H; or

R^1 and R^2 together form an optionally substituted 5-7 membered carbocyclic ring, aryl, or heteroaryl or heterocyclic ring comprising N, O and/or S; and

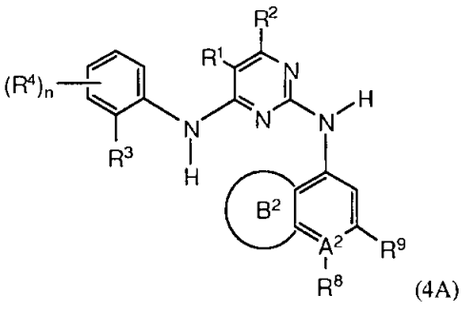
R^6 is isopropoxy or methoxy.

9. The compound of claim 8, wherein each R^{11} is $(CR_2)_pCO_{1-2}R$, $(CR_2)_pOR$, $(CR_2)_pR^{13}$, $(CR_2)_pNRR^{12}$ or $(CR_2)_pCONRR^{12}$;

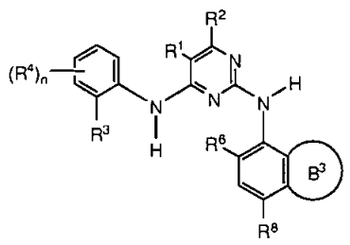
R and R^{12} are independently H or C_{1-6} alkyl; and

R^{13} is an optionally substituted piperidinyl, azetidiyl, tetrahydropyranyl, cyclohexyl, morpholinyl, pyrrolidinyl, heptamethyleneimine, octamethyleneimine, a bicyclic amine or diamine derivative, quinuclidin-3-yl, 8-methyl-8-aza-bicyclo[3.2.1]oct-6-yl], or 9-methyl-9-aza-bicyclo[4.2.1]nonan-7-yl.

10. The compound of claim 1, wherein said compound is of Formula (4A) or Formula (4B):



(4A)



(4B);

wherein R^1 is halo or C_{1-6} alkyl;

R^2 is H; or

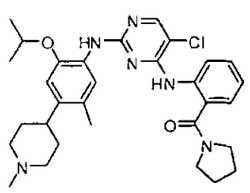
R^1 and R^2 together form an optionally substituted 5-7 membered carbocyclic ring, aryl, or heteroaryl or heterocyclic ring comprising N, O and/or S;

R^6 is isopropoxy or methoxy; and

B^2 and B^3 are independently an optionally substituted 5-6 membered aryl or heteroaryl containing N, O or S.

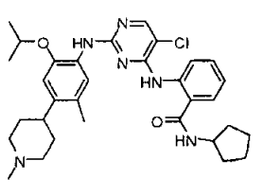
11. The compound of claim 1, wherein said compound is selected from the group consisting of

1



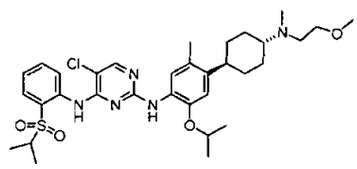
(2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino) pyrimidin-4-ylamino)phenyl)(pyrrolidin-1-yl)methanone

2



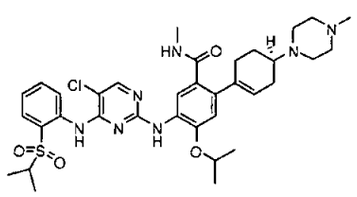
2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino) pyrimidin-4-ylamino)-N-cyclopentylbenzamide

124



N2-(4-((1r,4r)-4-(N-(2-methoxyethyl)-N-methylamino)cyclohexyl)-2-isopropoxy-5-methylphenyl)-5-chloro-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine

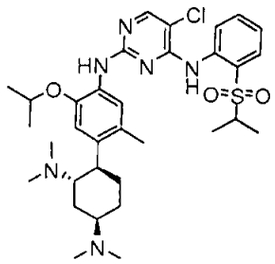
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5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-((R)-4-(4-methylpiperazin-1-yl)cyclohex-1-enyl)benzamide

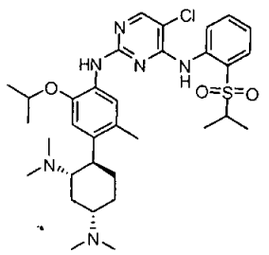
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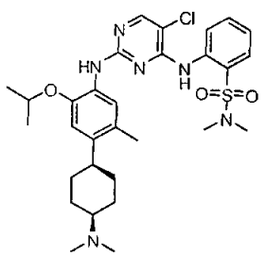
N2-(4-((1R,2S,4R)-2,4-bis(dimethylamino) cyclohexyl)-2-isopropoxy-5-methylphenyl)-5-chloro-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

4



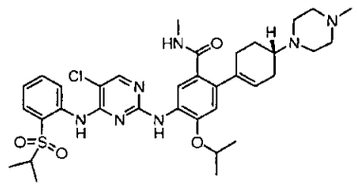
N2-(4-((1R,2S,4S)-2,4-bis(dimethylamino) cyclohexyl)-2-isopropoxy-5-methylphenyl)-5-chloro-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

5



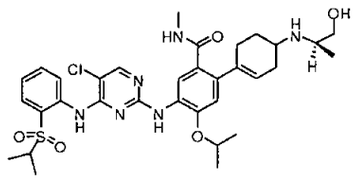
2-(5-chloro-2-(4-((1s,4s)-4-(dimethylamino) cyclohexyl)-2-isopropoxy-5-methylphenylamino) pyrimidin-4-ylamino)-N,Ndimethylbenzenesulfonamide

126



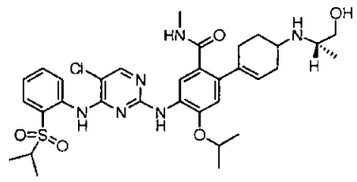
5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-((S)-4-(4-methylpiperazin-1-yl)cyclohex-1-enyl)benzamide

127



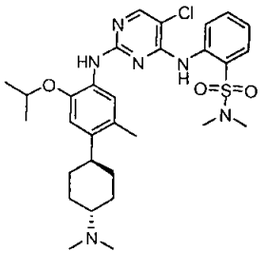
2-(4-((R)-1-hydroxypropan-2-ylamino)cyclohex-1-enyl)-5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methylbenzamide

128



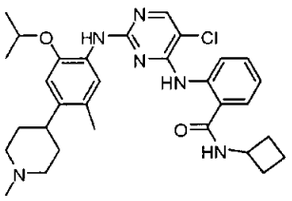
2-(4-((S)-1-hydroxypropan-2-ylamino)cyclohex-1-enyl)-5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methylbenzamide

6



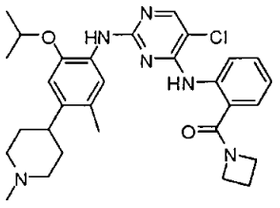
2-(5-chloro-2-(4-((1r,4r)-4-(dimethylamino)cyclohexyl)-2-isopropoxy-5-methylphenylamino) pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide

7



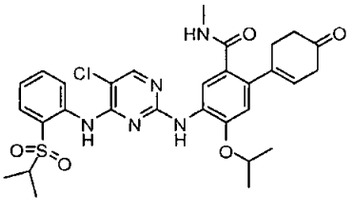
2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino) pyrimidin-4-ylamino)-N-cyclobutylbenzamide

8



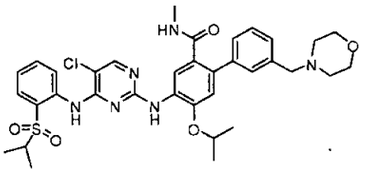
azetidin-1-yl(2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino) pyrimidin-4-ylamino)phenyl)methanone

129



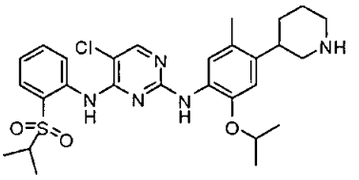
5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-(4-oxocyclohex-1-enyl)benzamide

130



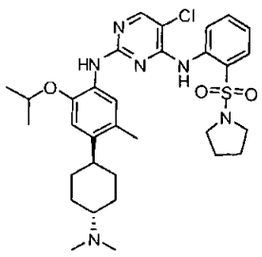
5-chloro-N4-(2-(isopropylsulfony)phenyl)-N2-(2-isopropoxy-5-(N-methylcarboxamido)-4-(3-methyl-4-(3-morpholinomethyl)-phenyl)pyrimidine-2,4-diamine

131



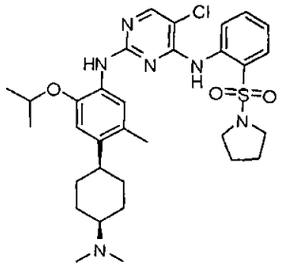
5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-3-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

9



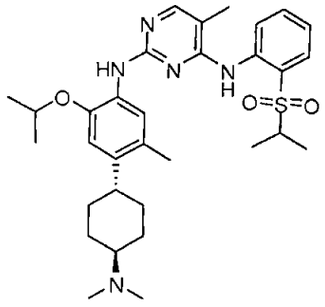
5-chloro-N2-(4-((1r,4r)-4-(dimethylamino) cyclohexyl)-2-isopropoxy-5-methylphenyl)-N4-(2-(pyrrolidin-1-ylsulfonyl)phenyl) pyrimidine-2,4-diamine

10



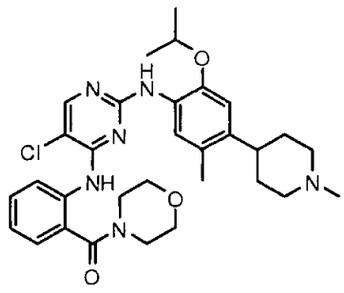
5-chloro-N2-(4-((1s,4s)-4-(dimethylamino) cyclohexyl)-2-isopropoxy-5-methylphenyl)-N4-(2-(pyrrolidin-1-ylsulfonyl)phenyl) pyrimidine-2,4-diamine

11



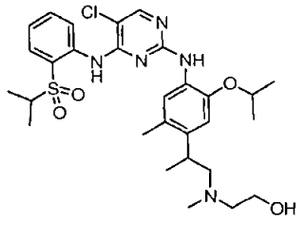
N2-(4-((1r,4r)-4-(dimethylamino)cyclohexyl)-2-isopropoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl) phenyl)-5-methylpyrimidine-2.4-diamine

132



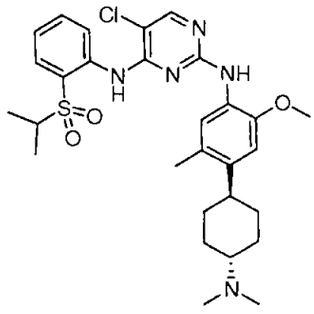
(2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)phenyl)(morpholino)methanone

133



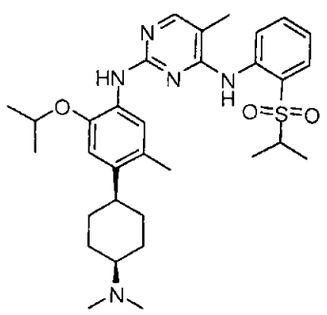
2-((2-(4-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyrimidin-2-ylamino)-5-isopropoxy-2-methylphenyl) propyl)(methyl)amino) ethanol

134



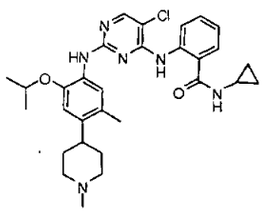
5-chloro-N2-(4-((1r,4r)-4-(dimethylamino) cyclohexyl)-2-methoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

12



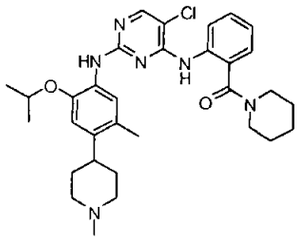
N2-(4-((1s,4s)-4-(dimethylamino) cyclohexyl)-2-isopropoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl) phenyl)-5-methylpyrimidine-2,4-diamine

13



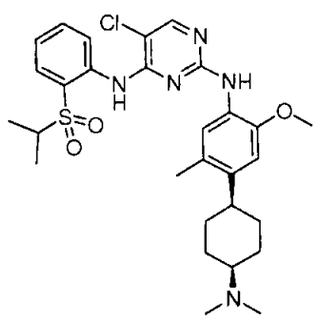
2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino) pyrimidin-4-ylamino)-N-cyclopropylbenzamide

14



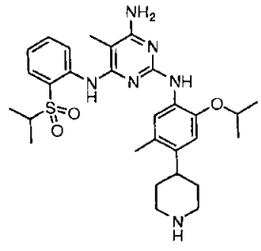
(2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino) pyrimidin-4-ylamino)phenyl)(piperidin-1-yl)methanone

135



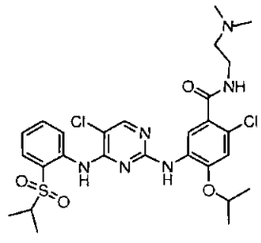
5-chloro-N2-(4-((1s,4s)-4-(dimethylamino) cyclohexyl)-2-methoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

136



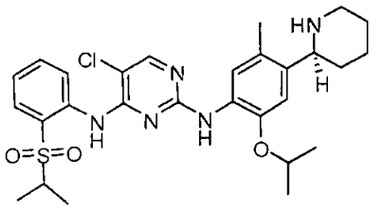
N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)-5-methylpyrimidine-2,4,6-triamine

137



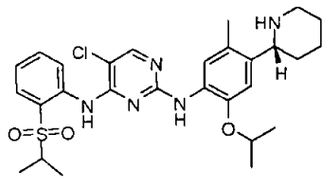
5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2-chloro-N-(2-(dimethylamino)ethyl)-4-isopropoxybenzamide

15



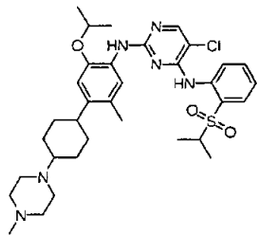
(S)-5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-2-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine

16



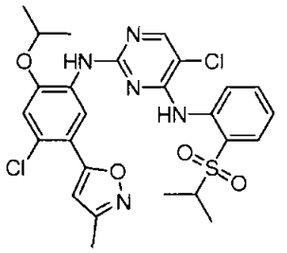
(R)-5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-2-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl) pyrimidine-2,4-diamine

17



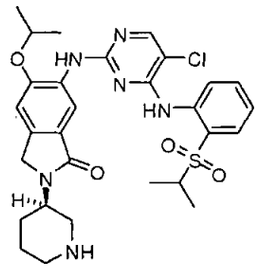
(*cis,trans*) 5-Chloro-N2-{2-isopropoxy-5-methyl-4-[4-(4-methyl-piperazin-1-yl)-cyclohexyl]-phenyl}-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine

138



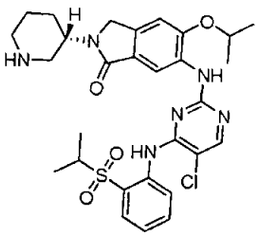
5-chloro-N2-(4-chloro-2-isopropoxy-5-(3-methylisoxazol-5-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine

139



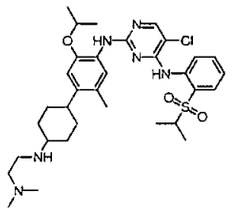
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-((R)-piperidin-3-yl)isoindolin-1-one

140



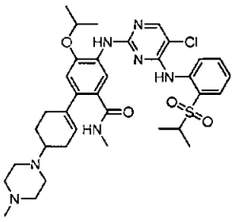
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-((S)-piperidin-3-yl)isoindolin-1-one

18



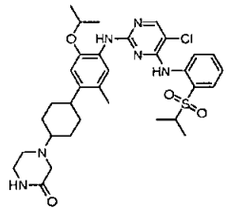
(*cis,trans*) 5-chloro-N2-{4-[4-(2-dimethylamino-ethyl amino)-cyclohexyl]-2-isopropoxy-5-methyl-phenyl}-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine

19



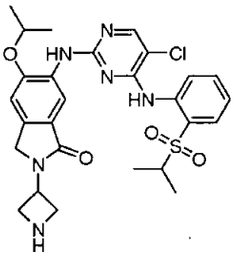
5-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-4-isopropoxy-N-methyl-2-[4-(4-methyl-piperazin-1-yl)-cyclohex-1-enyl]-benzamide

20



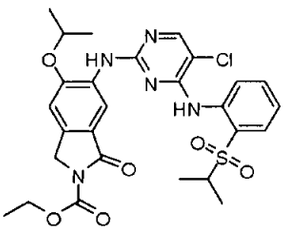
4-[4-(4-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-methyl-phenyl)-cyclohexyl]-piperazin-2-one

141



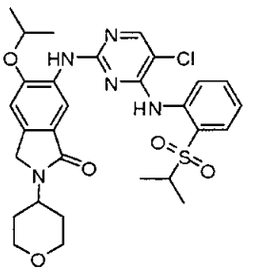
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2-(azetidin-3-yl)-5-isopropoxyisoindolin-1-one

142



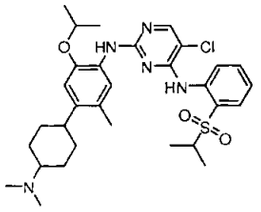
Ethyl 6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindoline-2-carboxylate

143



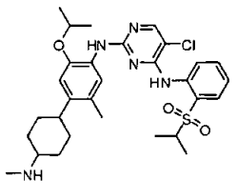
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2-(tetrahydro-2H-pyran-4-yl)-5-isopropoxyisoindolin-1-one

21



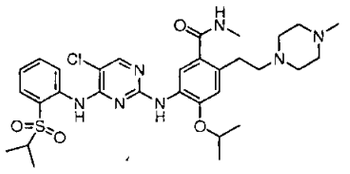
5-Chloro-N2-[4-(4-dimethylamino-cyclohexyl)-2-isopropoxy-5-methyl-phenyl]-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine

22



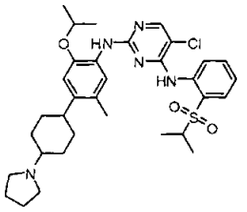
5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-methylamino-cyclohexyl)-phenyl]-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine

23



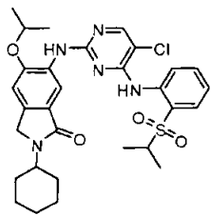
5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-(2-(4-methylpiperazin-1-yl)ethyl)benzamide

24



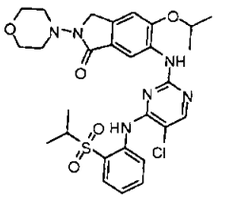
5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-pyrrolidin-1-yl-cyclohexyl)-phenyl]-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine

144



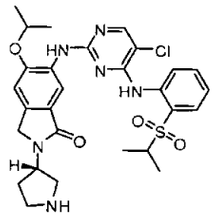
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloro pyrimidin-2-ylamino)-2-cyclohexyl-5-isopropoxy-isoindolin-1-one

145



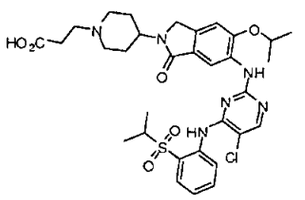
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloro pyrimidin-2-ylamino)-5-isopropoxy-2-morpholino-isoindolin-1-one

146



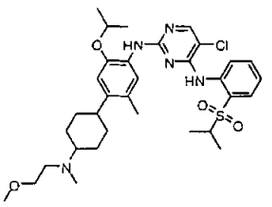
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-((S)-pyrrolidin-3-yl)isoindolin-1-one

147



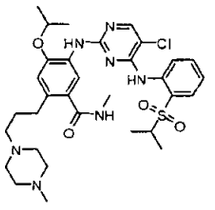
3-(4-(6-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)piperidin-1-yl)propanoic acid

25



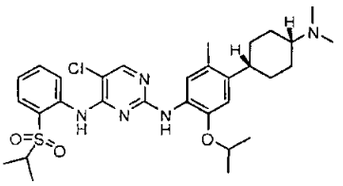
5-Chloro-N2-(2-isopropoxy-4-{4-[(2-methoxy-ethyl)-methyl-amino]-cyclohexyl}-5-methyl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine

26



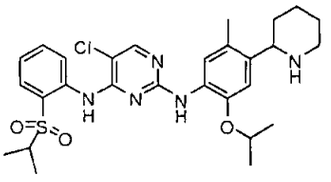
5-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-4-isopropoxy-N-methyl-2-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide

27



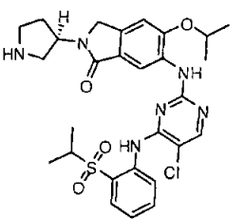
5-chloro-N2-(4-((1s,4s)-4-(dimethylamino) cyclohexyl)-2-isopropoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine

28



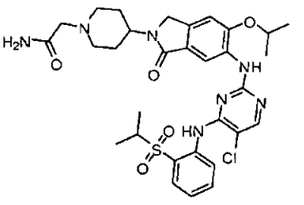
5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-2-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine

148



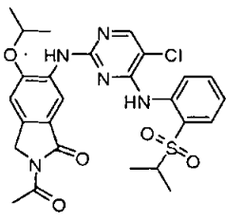
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-((R)-pyrrolidin-3-yl)isoindolin-1-one

149



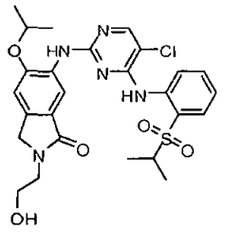
2-[4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenyl-amino]-pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidin-1-yl]-acetamide

150



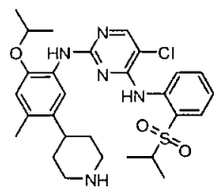
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2-acetyl-5-isopropoxyisoindolin-1-one

151



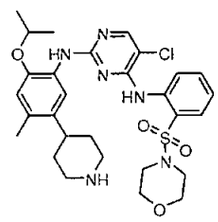
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2-(2-hydroxyethyl)-5-isopropoxyisoindolin-1-one

29



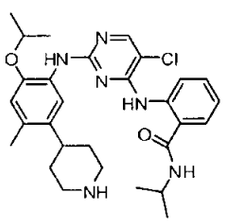
5-chloro-N2-(2-isopropoxy-4-methyl-5-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl) pyrimidine-2,4-diamine

30



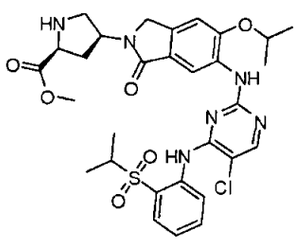
5-chloro-N2-(2-isopropoxy-4-methyl-5-(piperidin-4-yl)phenyl)-N4-(2(morpholinosulfonamido) phenyl)pyrimidine-2,4-diamine

31



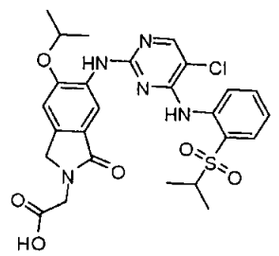
2-(2-(2-isopropoxy-4-methyl-5-(piperidin-4-yl)phenylamino)-5-chloropyrimidin-4-ylamino)-N-isopropylbenzamide

152



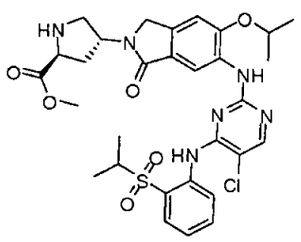
(2S,4S)-methyl 4-(6-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)pyrrolidine-2-carboxylate

153



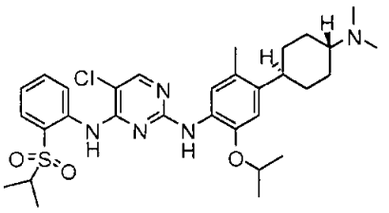
2-(6-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)acetic acid

154



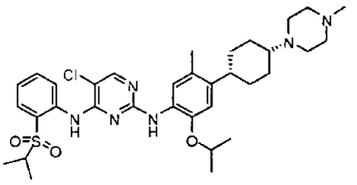
(2S,4R)-methyl 4-(6-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)pyrrolidine-2-carboxylate

32



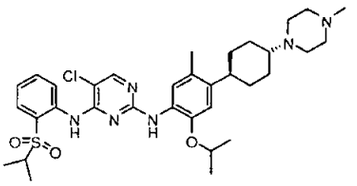
5-chloro-N2-(4-((1r,4r)-4-(dimethylamino) cyclohexyl)-2-isopropoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine

33



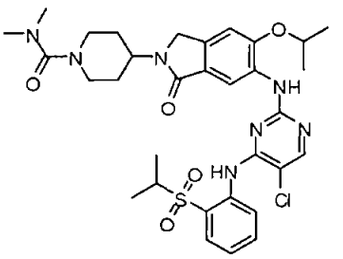
5-chloro-N2-(2-isopropoxy-5-methyl-4-((1s,4s)-4-(4-methylpiperazin-1-yl)cyclohexyl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine

34



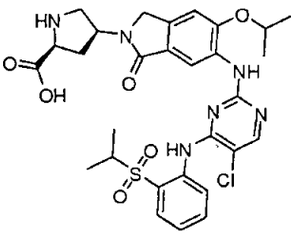
5-chloro-N2-(2-isopropoxy-5-methyl-4-((1r,4r)-4-(4-methylpiperazin-1-yl)cyclohexyl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine

155



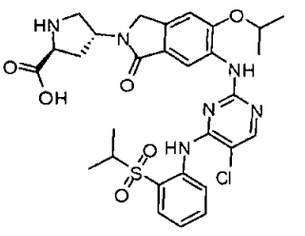
4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid dimethylamide

156



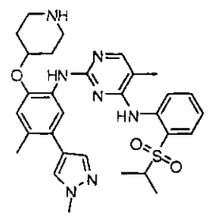
(2S,4S)-4-(6-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)pyrrolidine-2-carboxylic acid

157



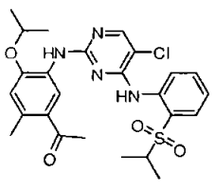
(2S,4R)-4-(6-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)pyrrolidine-2-carboxylic acid

35



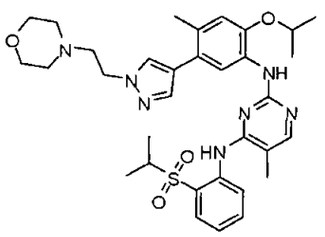
5-Methyl-N2-[4-methyl-5-(1-methyl-1H-pyrazol-4-yl)-2-(piperidin-4-yloxy)-phenyl]-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine

36



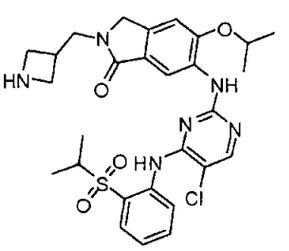
1-(5-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-4-isopropoxy-2-methyl-phenyl)-ethanone

37



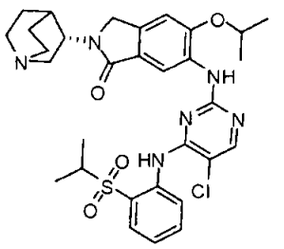
N2-{2-Isopropoxy-4-methyl-5-[1-(2-morpholin-4-yl-ethyl)-1H-pyrazol-4-yl]-phenyl}-5-methyl-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine

158



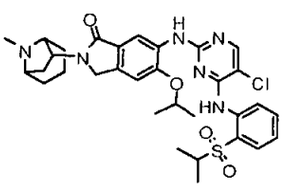
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2-((azetidin-3-yl)methyl)-5-isopropoxyisoindolin-1-one

159



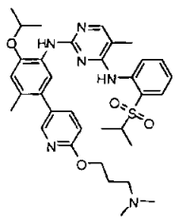
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-((S)-quinuclidin-3-yl)isoindolin-1-one

160



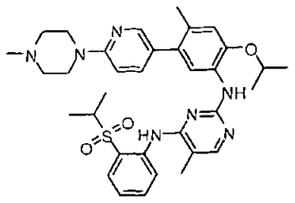
6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-yl)-2,3-dihydro-isoindol-1-one

38



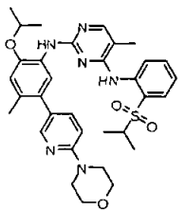
N2-(5-(6-(3-(dimethylamino)propoxy) pyridin-3-yl)-2-isopropoxy-4-methylphenyl)-N4-(2-(isopropyl sulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine

39



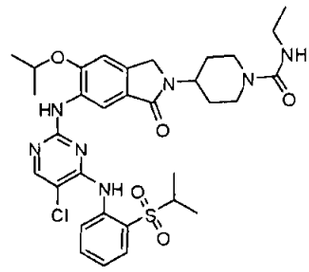
N2-(2-isopropoxy-4-methyl-5-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)-5-methylpyrimidine-2,4-diamine

40



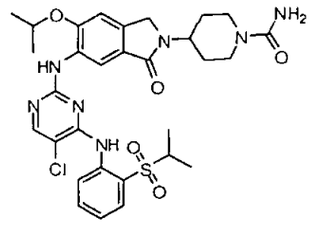
N2-(2-isopropoxy-4-methyl-5-(6-morpholinopyridin-3-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-5-methylpyrimidine-2,4-dianine

161



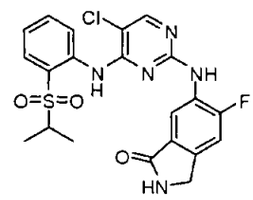
4-(6-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)-N-ethylpiperidine-1-carboxamide

162



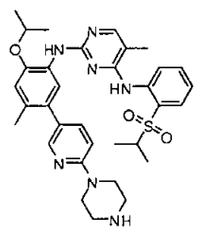
4-(6-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)piperidine-1-carboxamide

163



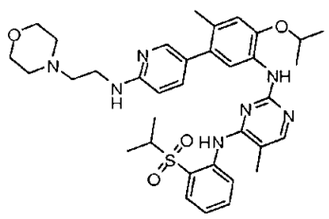
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-fluoroisoindolin-1-one

41



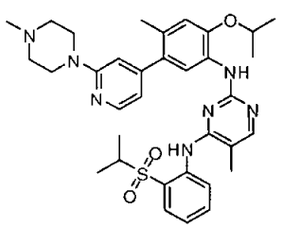
N2-(2-isopropoxy-4-methyl-5-(6-(piperazin-1-yl)pyridin-3-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)-5-methylpyrimidine-2,4-diamine

42



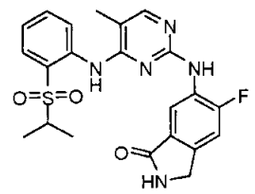
N2-(5-(6-(2-morpholinoethylamino) pyridin-3-yl)-2-isopropoxy-4-methylphenyl)-N4-(2-(isopropyl-sulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine

43



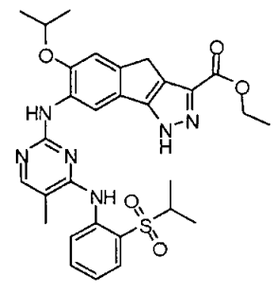
N2-(2-isopropoxy-4-methyl-5-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)-5-methylpyrimidine-2,4-diamine

164



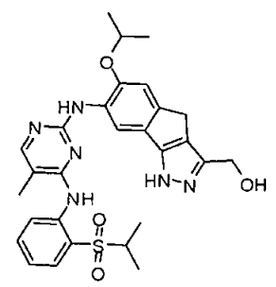
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-methylpyrimidin-2-ylamino)-5-fluoroisoindolin-1-one

165



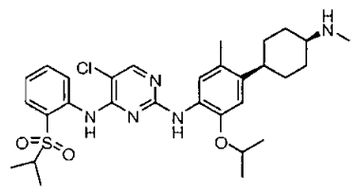
Ethyl 7-(4-(2-(isopropylsulfonyl) phenylamino)-5-methylpyrimidin-2-ylamino)-1,4-dihydro-6-isopropoxyindeno[1,2-c]pyrazole-3-carboxylate

166



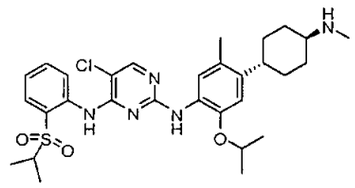
(7-(4-(2-(isopropylsulfonyl)phenylamino)-5-methylpyrimidin-2-ylamino)-1,4-dihydro-6-isopropoxyindeno[1,2-c]pyrazol-3-yl)methanol

44



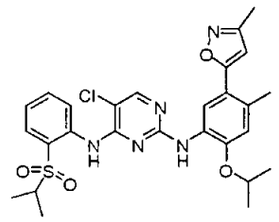
5-chloro-N2-(2-isopropoxy-5-methyl-4-((1s,4s)-4-(methylamino)cyclohexyl) phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

45



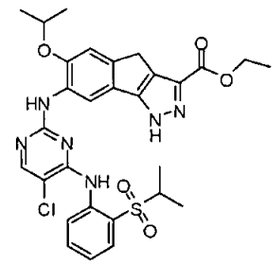
5-chloro-N2-(2-isopropoxy-5-methyl-4-((1r,4r)-4-(methylamino)cyclohexyl) phenyl)-N4-(2-(isopropylsulfonyl)phenyl) pyrimidine-2,4-diamine

46



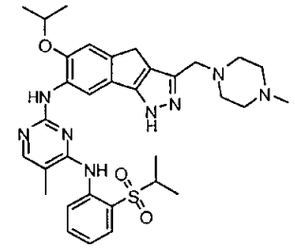
5-chloro-N2-(2-isopropoxy-4-methyl-5-(3-methylisoxazol-5-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine

167



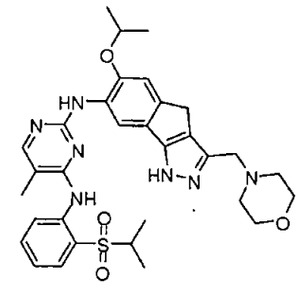
Ethyl 7-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-1,4-dihydro-6-isopropoxyindeno[1,2-c]pyrazole-3-carboxylate

168



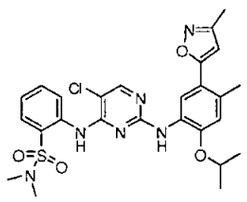
N2-(1,4-dihydro-6-isopropoxy-3-((4-methylpiperazin-1-yl)methyl)indeno[1,2-c]pyrazol-7-yl)-N4-(2-(isopropylsulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine

169



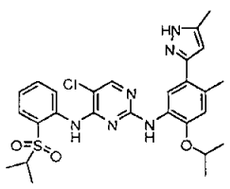
N2-(1,4-dihydro-6-isopropoxy-3-(morpholinomethyl) indeno[1,2-c]pyrazol-7-yl)-N4-(2-(isopropylsulfonyl) phenyl)-5-methylpyrimidine-2,4-diamine

47



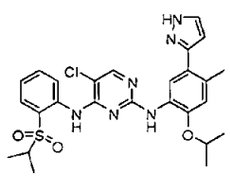
2-(5-chloro-2-(2-isopropoxy-4-methyl-5-(3-methylisoxazol-5-yl)phenylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide

48



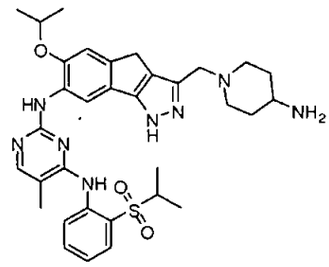
5-chloro-N2-(2-isopropoxy-4-methyl-5-(5-methyl-1H-pyrazol-3-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

49



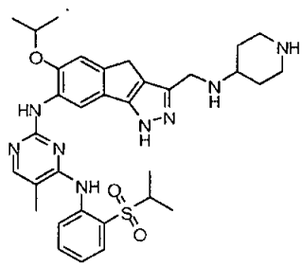
5-chloro-N2-(2-isopropoxy-4-methyl-5-(1H-pyrazol-3-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

170



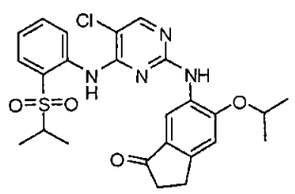
N2-(3-((4-aminopiperidin-1-yl)methyl)-1,4-dihydro-6-isopropoxyindeno[1,2-c]pyrazol-7-yl)-N4-(2-(isopropylsulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine

171



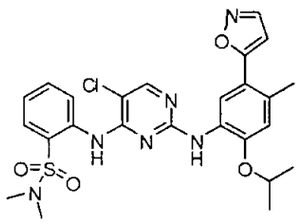
N2-(1,4-dihydro-6-isopropoxy-3-((piperidin-4-ylamino)methyl)indeno[1,2-c]pyrazol-7-yl)-N4-(2-(isopropylsulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine

172



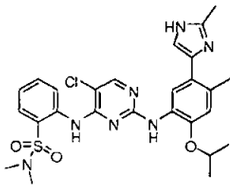
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2,3-dihydro-5-isopropoxyinden-1-one

50



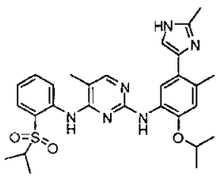
2-(5-chloro-2-(2-isopropoxy-5-(isoxazol-5-yl)-4-methylphenylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide

51



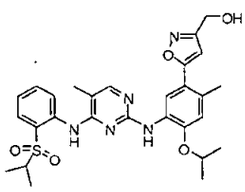
2-(5-chloro-2-(2-isopropoxy-4-methyl-5-(2-methyl-1H-imidazol-4-yl) phenylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide

52



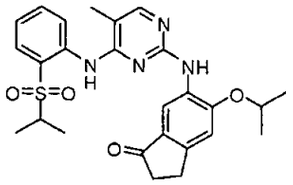
5-chloro-N2-(2-isopropoxy-4-methyl-5-(2-methyl-1H-imidazol-4-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

53



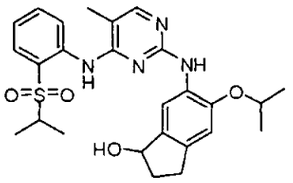
(5-(5-(4-(2-(isopropylsulfonyl) phenylamino)-5-methylpyrimidin-2-ylamino)-4-isopropoxy-2-methylphenyl)isoxazol-3-yl)methanol

173



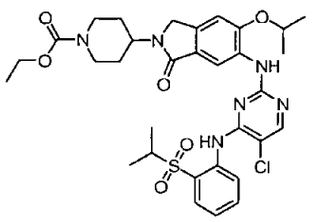
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-methylpyrimidin-2-ylamino)-2,3-dihydro-5-isopropoxyinden-1-one

174



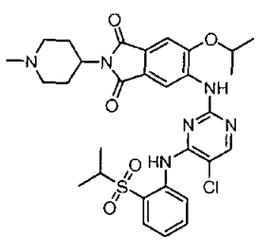
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-methyl pyrimidin-2-ylamino)-2,3-dihydro-5-isopropoxy-1H-inden-1-ol

175



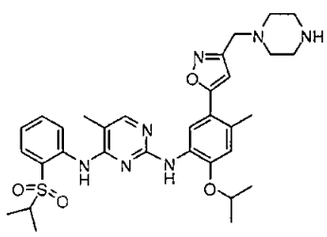
4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino] -pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro -isoindol-2-yl)-piperidine-1-carboxylic acid ethyl ester

176



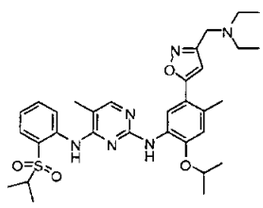
5-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-6-isopropoxy-2-(1-methyl-piperidin-4-yl)-isoindole-1,3-dione

54



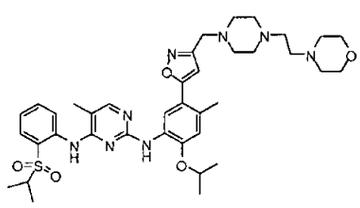
N2-(2-isopropoxy-4-methyl-5-(3-((piperazin-1-yl)methyl)isoxazol-5-yl)phenyl)-N4-(2-(isopropyl-sulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine

55



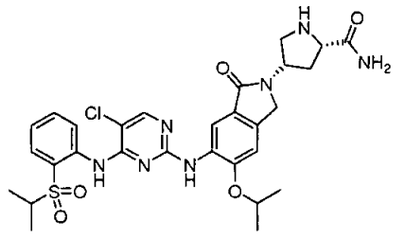
N2-(5-(3-((diethylamino)methyl) isoxazol-5-yl)-2-isopropoxy-4-methylphenyl)-N4-(2-(isopropyl-sulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine

56



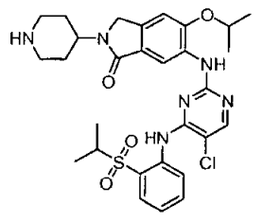
N2-(2-isopropoxy-4-methyl-5-(3-((4-(2-morpholinoethyl)piperazin-1-yl)methyl)isoxazol-5-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine

177



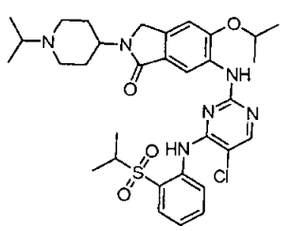
(2S, 4S)-4-(6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-1-oxo-1,3-dihydro-isoindol-2-yl)-pyrrolidine-2-carboxylic acid amide

178



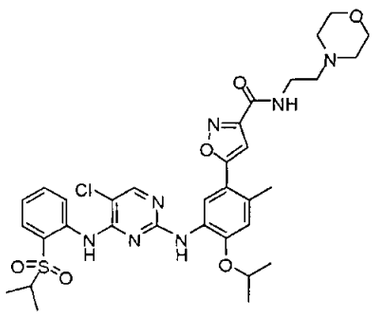
6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-piperidin-4-yl-2,3-dihydro-isoindol-1-one

179



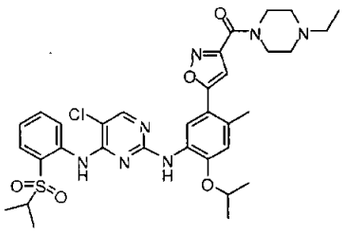
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-(1-isopropylpiperidin-4-yl)isoindolin-1-one

57



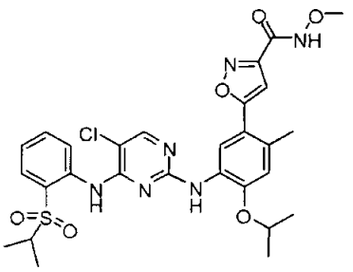
5-(5-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-2-methylphenyl)-N-(2-morpholinoethyl)isoxazole-3-carboxamide

58



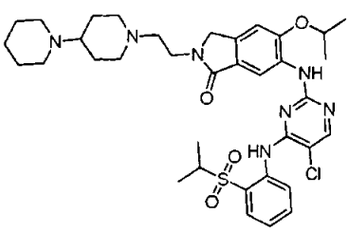
(5-(5-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-2-methylphenyl)isoxazol-3-yl)(4-ethylpiperazin-1-yl)methanone

59



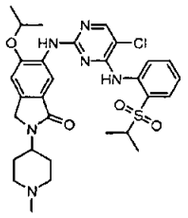
5-(5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-2-methylphenyl)-N-methoxyisoxazole-3-carboxamide

180



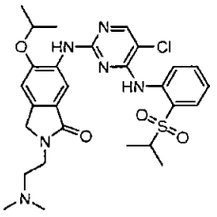
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-(2-(4-(piperidin-1-yl)piperidin-1-yl)ethyl)isoindolin-1-one

181



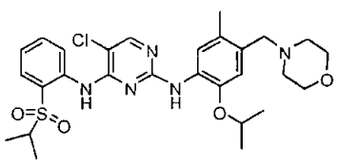
6-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-(1-methyl-piperidin-4-yl)-2,3-dihydro-isoindol-1-one

182



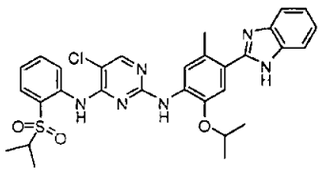
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloro pyrimidin-2-ylamino)-2-(1-(2-(dimethylamino)ethyl) piperidin-4-yl)-5-isopropoxyisoindolin-1-one

60



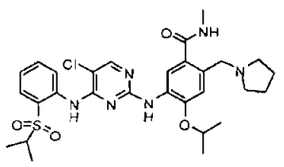
5-Chloro-N2-(2-isopropoxy-5-methyl-4-morpholin-4-ylmethyl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine

61



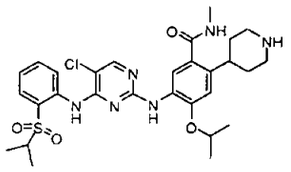
N2-(4-(1H-benzo[d]imidazol-2-yl)-2-isopropoxy-5-methylphenyl)-5-chloro-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

62



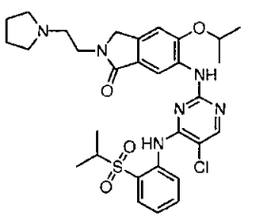
5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-((pyrrolidin-1-yl)methyl)benzamide

63



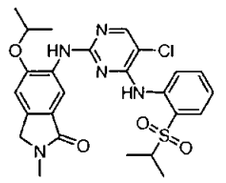
5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-(piperidin-4-yl)benzamide

183



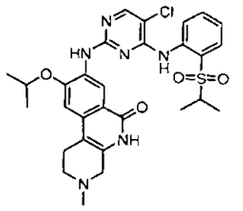
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-(1-(2-(pyrrolidin-1-yl)ethyl)piperidin-4-yl)isoindolin-1-one

184



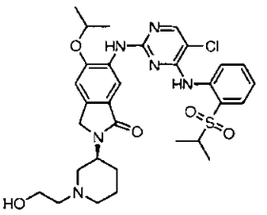
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-methylisoindolin-1-one

185



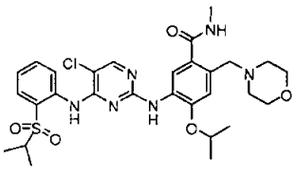
8-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino) pyrimidin-2-ylamino)-9-isopropoxy-3-methyl-1,2,3,4-tetrahydrobenzo[c][1,7]naphthyridin-6(5H)-one

186



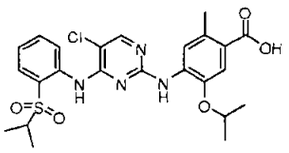
(S)-6-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino) pyrimidin-2-ylamino)-2-(1-(2-hydroxyethyl)piperidin-3-yl)-5-isopropoxyisoindolin-1-one

64



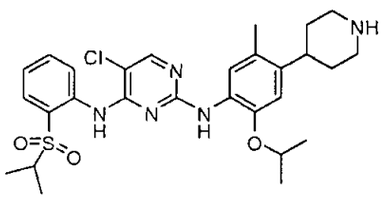
5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-(morpholinomethyl)benzamide

65



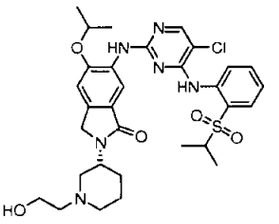
4-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-methylbenzoic acid

66



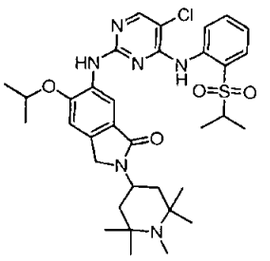
5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine

187



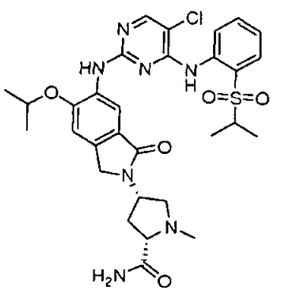
(R)-6-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyrimidin-2-ylamino)-2-(1-(2-hydroxyethyl)piperidin-3-yl)-5-isopropoxyisoindolin-1-one

188



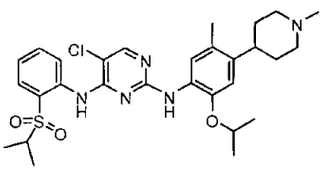
6-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino) pyrimidin-2-ylamino)-5-isopropoxy-2-(1,2,2,6,6-pentamethyl piperidin-4-yl)isoindolin-1-one

189



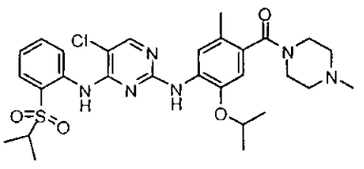
(2S,4S)-4-(6-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino) pyrimidin-2-ylamino)-5-isopropoxy-1-oxoisoindolin-2-yl)-1-methylpyrrolidine-2-carboxamide

67



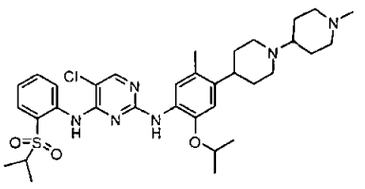
5-chloro-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-[2-(propane-2-sulfonyl)phenyl]-pyrimidine-2,4-diamine

68



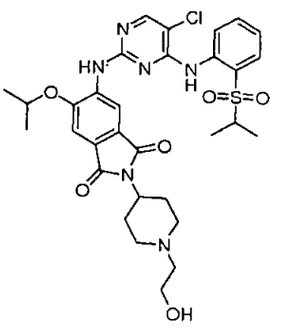
(4-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-methylphenyl)(4-methylpiperazin-1-yl)methanone

69



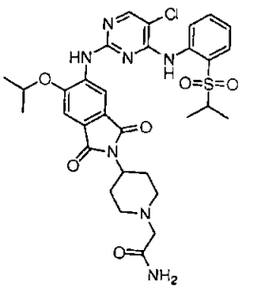
5-chloro-N2-(2-isopropoxy-5-methyl-4-(1-(1-methylpiperidin-4-yl)piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2.4-diamine

190



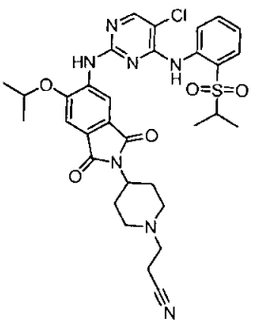
5-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino) pyrimidin-2-ylamino)-2-(1-(2-hydroxyethyl)piperidin-4-yl)-6-isopropoxyisoindoline-1,3-dione

191



2-(4-(5-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino) pyrimidin-2-ylamino)-6-isopropoxy-1,3-dioxoisoindolin-2-yl)piperidin-1-yl)acetamide

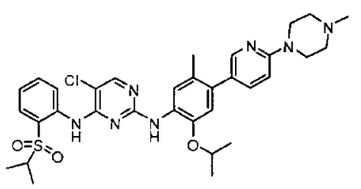
192



3-(4-(5-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino)pyrimidin-2-ylamino)-6-isopropoxy-1,3-dioxoisoindolin-2-yl)piperidin-1-yl)propanenitrile

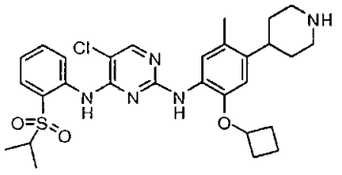
181

70



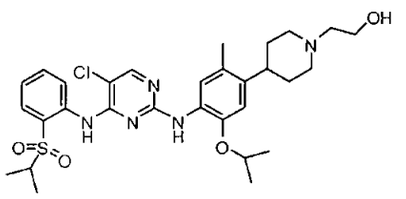
5-chloro-N2-(2-isopropoxy-5-methyl-4-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

71



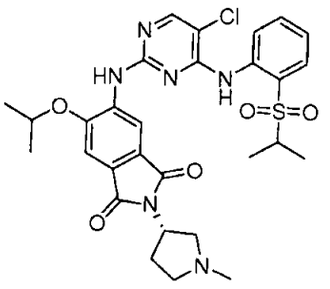
5-chloro-N2-(2-cyclobutoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine

72



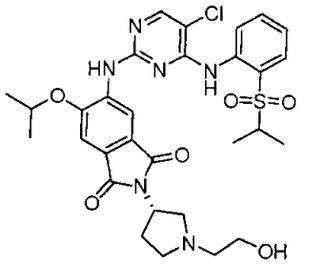
2-[4-(4-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-5-isopropoxy-2-methyl-phenyl)-piperidin-1-yl]-ethanol

193



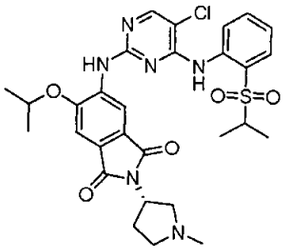
(S)-5-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino) pyrimidin-2-ylamino)-6-isopropoxy-2-(1-methylpyrrolidin-3-yl)isoindoline-1,3-dione

194



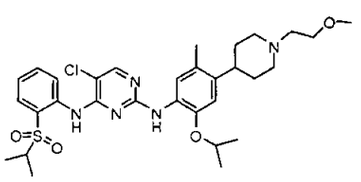
(S)-5-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino) pyrimidin-2-ylamino)-2-(1-(2-hydroxyethyl)pyrrolidin-3-yl)-6-isopropoxyisoindoline-1,3-dione

195



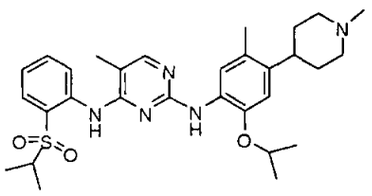
(S)-5-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino) pyrimidin-2-ylamino)-6-isopropoxy-2-(1-methylpyrrolidin-3-yl)isoindoline-1,3-dione

73



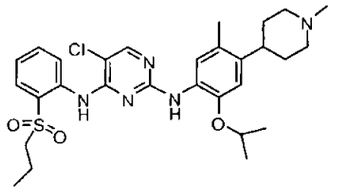
5-chloro-N2-(2-isopropoxy-4-(1-(2-methoxyethyl)piperidin-4-yl)-5-methylphenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

74



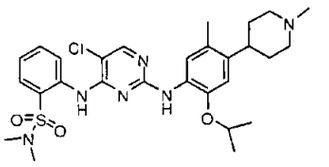
N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine

75



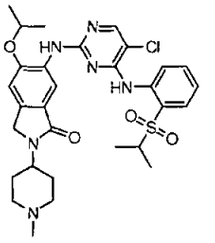
5-chloro-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(propylsulfonyl)phenyl)pyrimidine-2,4-diamine

76



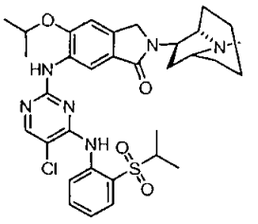
2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino) pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide

196



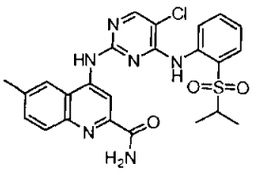
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-(1-methylpiperidin-4-yl)isoindolin-1-one

197



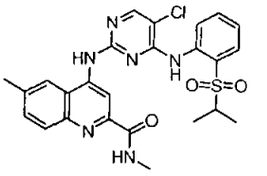
6-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-((6S.7R)-9-methyl-9-aza-bicyclo[4.2.1]nonan-7-yl)isoindolin-1-one

198



4-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-6-methyl-quinoline-2-carboxylic acid amide

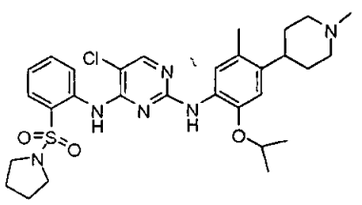
199



4-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-6-methyl-quinoline-2-carboxylic acid methylamide

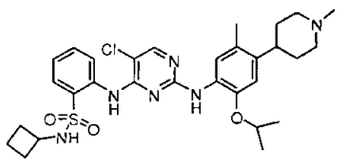
183

77



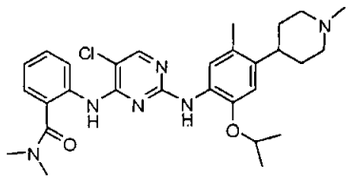
5-chloro-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(pyrrolidin-1-ylsulfonyl)phenyl) pyrimidine-2.4-diamine

78



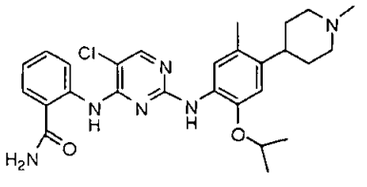
5-chloro-N4-(2-(cyclobutylaminosulfonyl)phenyl)-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)pyrimidine-2,4-diamine

79



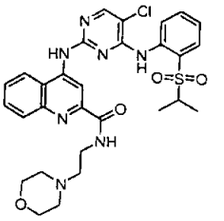
2-(2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)-5-chloropyrimidin-4-ylamino)-N,N-dimethylbenzamide

80



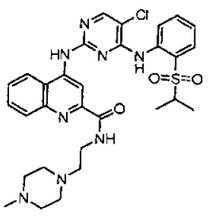
2-(2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)-5-chloropyrimidin-4-ylamino) benzamide

200



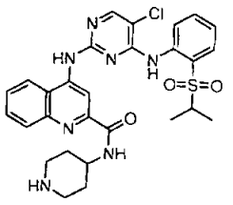
4-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-quinoline-2-carboxylic acid (2-morpholin-4-yl-ethyl)-amide

201



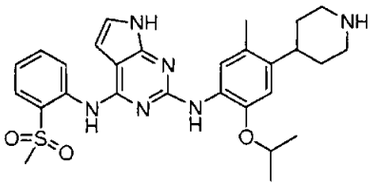
4-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-quinoline-2-carboxylic acid [2-(4-methyl-piperazin-1-yl)-ethyl]-amide

202



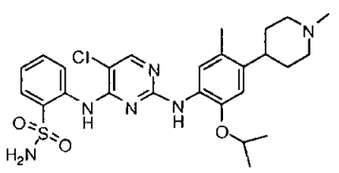
4-{5-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-pyrimidin-2-ylamino}-quinoline-2-carboxylic acid piperidin-4-ylamide

203



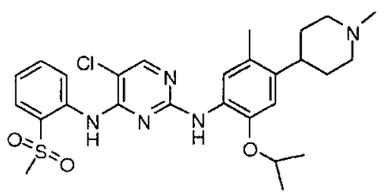
N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(methylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

81



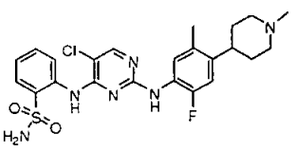
5-chloro-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(aminosulfonyl)phenyl)pyrimidine-2,4-diamine

82



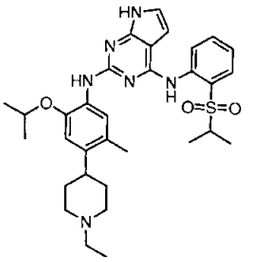
5-chloro-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(methylsulfonyl)phenyl)pyrimidine-2,4-diamine

83



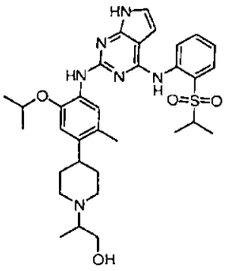
5-chloro-N2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(aminosulfonyl)phenyl)pyrimidine-2,4-diamine

204



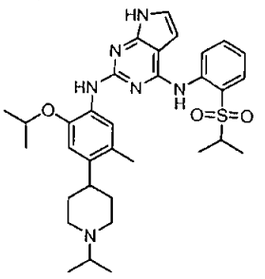
N2-(4-(1-ethylpiperidin-4-yl)-2-isopropoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

205



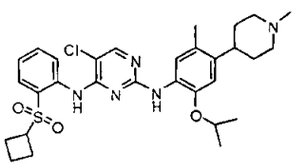
2-(4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)piperidin-1-yl)propan-1-ol

206



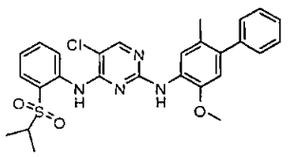
N2-(2-isopropoxy-4-(1-isopropylpiperidin-4-yl)-5-methylphenyl)-N4-(2-(isopropylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

84



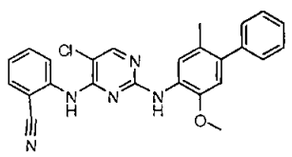
5-chloro-N4-(2-(cyclobutylsulfonyl)phenyl)-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)pyrimidine-2,4-diamine

85



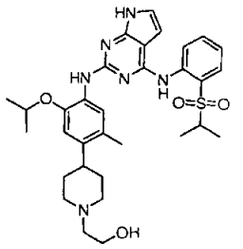
5-chloro-N4-(2-(isopropylsulfonyl) phenyl)-N2-(2-methoxy-5-methyl-4-phenyl)-phenyl)pyrimidine-2,4-diamine

86



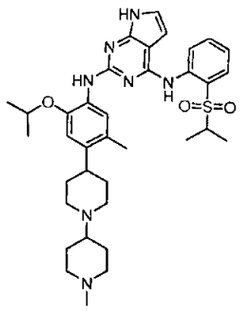
5-chloro-N4-(2-cyanophenyl)-N2-(2-methoxy-5-methyl-4-phenyl)-phenyl)pyrimidine-2,4-diamine

207



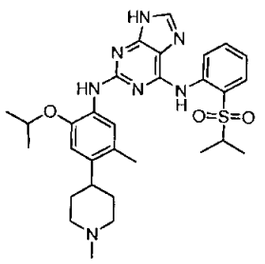
2-(4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)piperidin-1-yl)ethanol

208



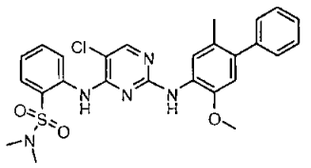
N2-(2-isopropoxy-5-methyl-4-(1'-methyl-1,4'-bipiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

209



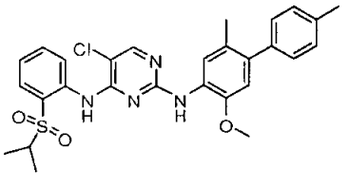
N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N6-(2-(isopropylsulfonyl)phenyl)-9H-purine-2,6-diamine

87



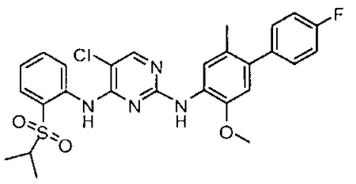
2-(5-chloro-2-(5-methoxy-2-methylbiphenyl-4-ylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide

88



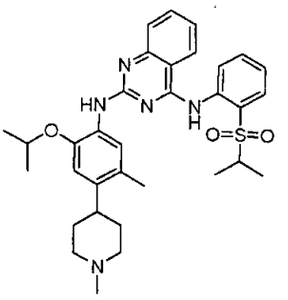
5-chloro-N4-(2-(isopropylsulfonyl) phenyl)-N2-(2-methoxy-5-methyl-4-(4-methylphenyl)-phenyl)pyrimidine-2,4-diamine

89



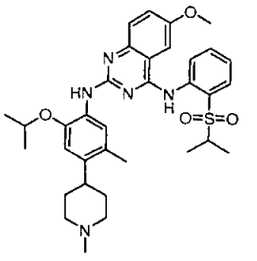
5-chloro-N4-(2-(isopropylsulfonyl) phenyl)-N2-(2-methoxy-5-methyl-4-(4-fluorophenyl)-phenyl)pyrimidine-2,4-diamine

210



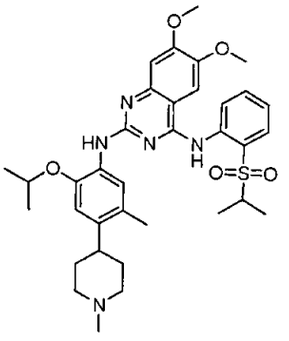
N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)quinazoline-2,4-diamine

211



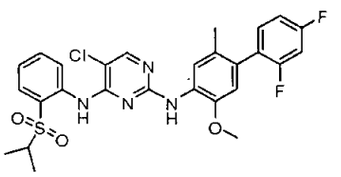
N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-6-methoxyquinazoline-2,4-diamine

212



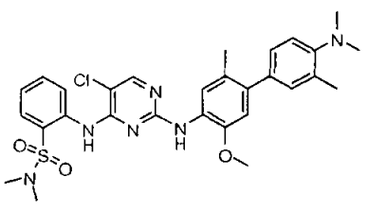
N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-6,7-dimethoxyquinazoline-2,4-diamine

90



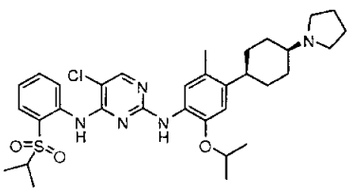
5-chloro-N4-(2-(isopropylsulfonyl) phenyl)-N2-(2-methoxy-5-methyl-4-(2,4-difluorophenyl)-phenyl)pyrimidine-2,4-diamine

91



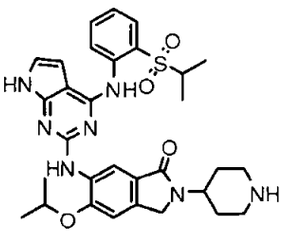
2-(5-chloro-2-(4'-(dimethylamino)-5-methoxy-2,3'-dimethylbiphenyl-4-ylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide

92



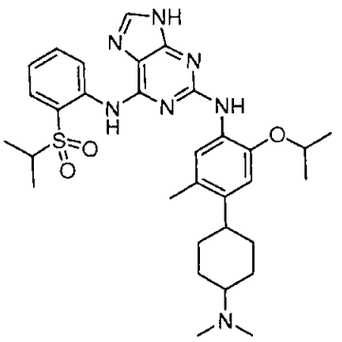
5-chloro-N2-(2-isopropoxy-5-methyl-4-((1s,4s)-4-(pyrrolidin-1-yl)cyclohexyl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine

213



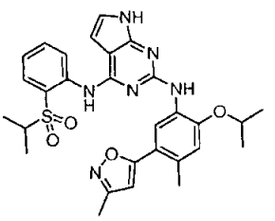
5-isopropoxy-6-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-(piperidin-4-yl)isoindolin-1-one

214



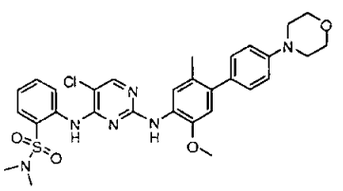
N2-(4-(4-(dimethylamino)cyclohexyl)-2-isopropoxy-5-methylphenyl)-N6-(2-(isopropylsulfonyl)phenyl)-9H-purine-2,6-diamine

215



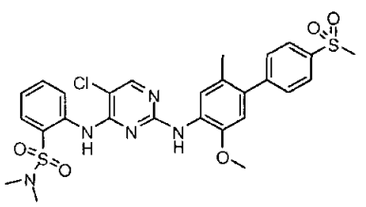
N2-(2-isopropoxy-4-methyl-5-(3-methylisoxazol-5-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

93



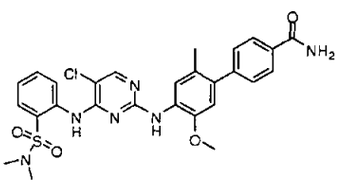
2-(5-chloro-2-(5-methoxy-2-methyl-4'-morpholinobiphenyl-4-ylamino) pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide

94



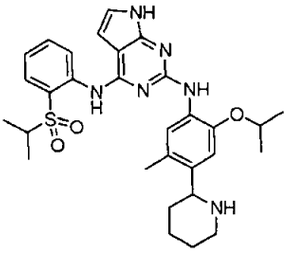
2-(5-chloro-2-(5-methoxy-2-methyl-4'-(methylsulfonyl)biphenyl-4-ylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide

95



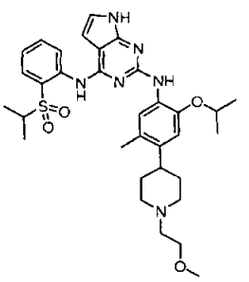
4'-(5-chloro-4-(2-(N,N-dimethylsulfamoyl) phenylamino) pyrimidin-2-ylamino)-5'-methoxy-2'-methylbiphenyl-4-carboxamide

216



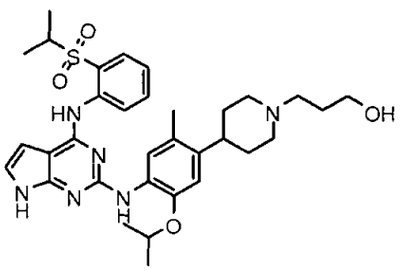
N2-(2-isopropoxy-5-methyl-4-(piperidin-2-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

217



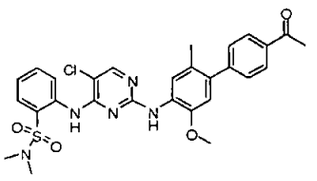
N2-(2-isopropoxy-4-(1-(2-methoxyethyl)piperidin-4-yl)-5-methylphenyl)-N4-(2-(isopropylsulfonyl) phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

218



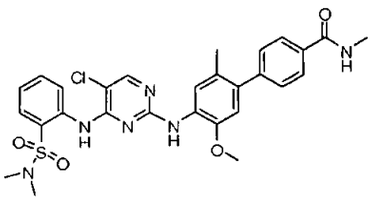
3-(4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)piperidin-1-yl)propan-1-ol

96



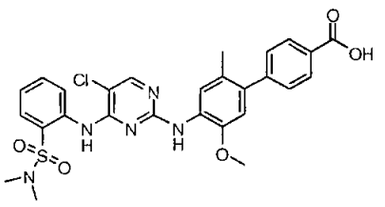
2-(2-(4'-acetyl-5-methoxy-2-methylbiphenyl-4-ylamino)-5-chloropyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide

97



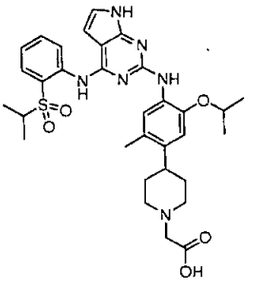
4'-(5-chloro-4-(2-(N,N-dimethylsulfamoyl) phenylamino) pyrimidin-2-ylamino)-5'-methoxy-N,2'-dimethylbiphenyl-4-carboxamide

98



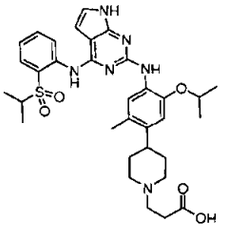
4'-(5-chloro-4-(2-(N,N-dimethylsulfamoyl) phenylamino) pyrimidin-2-ylamino)-5'-methoxy-2'-methylbiphenyl-4-carboxylic acid

219



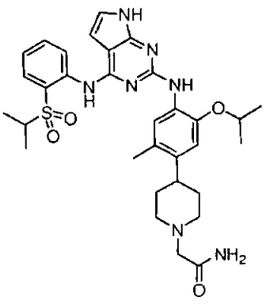
2-(4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)piperidin-1-yl)acetic acid

220



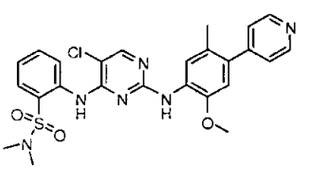
3-(4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)piperidin-1-yl)propanoic acid

221



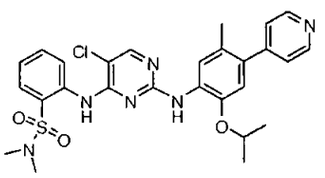
2-(4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)piperidin-1-yl)acetamide

99



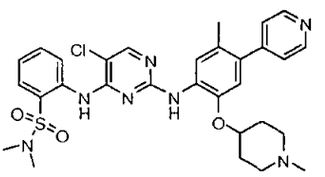
2-(5-chloro-2-(2-methoxy-5-methyl-4-(pyridin-4-yl)phenylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide

100



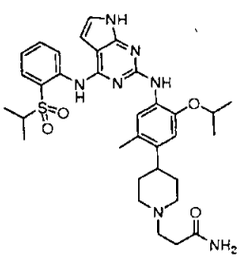
2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(pyridin-4-yl)phenylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide

101



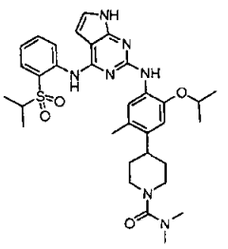
2-(5-chloro-2-(5-methyl-2-(1-methylpiperidin-4-yloxy)-4-(pyridin-4-yl)phenylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide

222



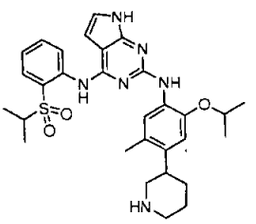
3-(4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)piperidin-1-yl)propanamide

223



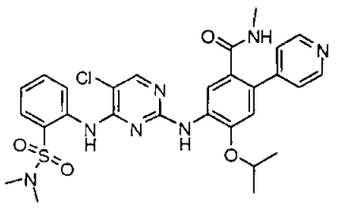
4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)-N,N-dimethylpiperidine-1-carboxamide

224



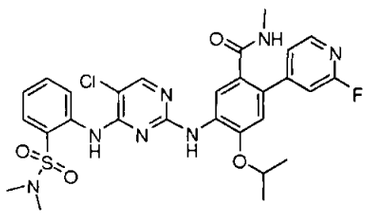
N2-(2-isopropoxy-5-methyl-4-(piperidin-3-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

102



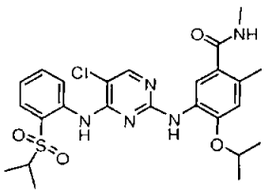
5-(5-chloro-4-(2-(N,N-dimethylsulfamoyl) phenylamino) pyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-(pyridin-4-yl)benzamide

103



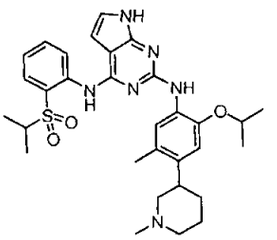
5-(5-chloro-4-(2-(N,N-dimethylsulfamoyl) phenylamino) pyrimidin-2-ylamino)-2-(2-fluoropyridin-4-yl)-4-isopropoxy-N-methylbenzamide

104



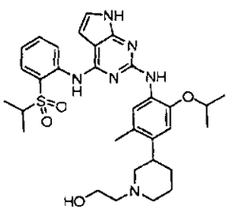
5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N,2-dimethylbenzamide

225



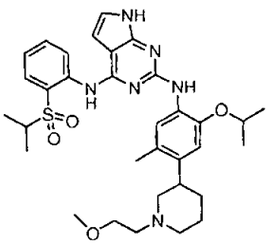
N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-3-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

226



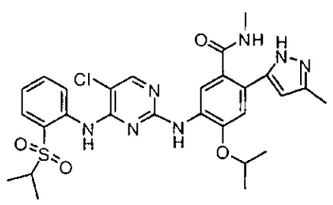
2-(3-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)piperidin-1-yl)ethanol

227



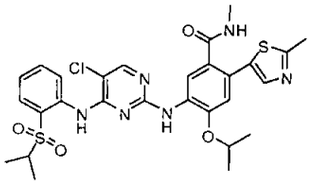
N2-(2-isopropoxy-4-(1-(2-methoxyethyl)piperidin-3-yl)-5-methylphenyl)-N4-(2-(isopropylsulfonyl) phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

105



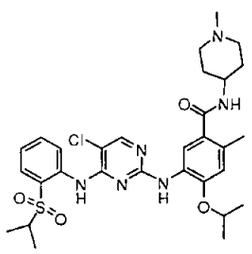
5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-(3-methyl-1H-pyrazol-5-yl)benzamide

106



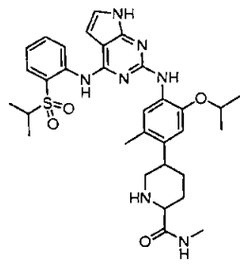
5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-N-methyl-2-(2-methylthiazol-5-yl)benzamide

107



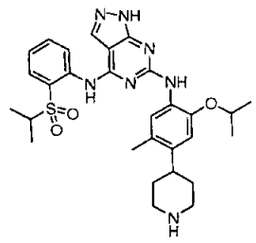
5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-4-isopropoxy-2-methyl-N-(1-methylpiperidin-4-yl)benzamide

228



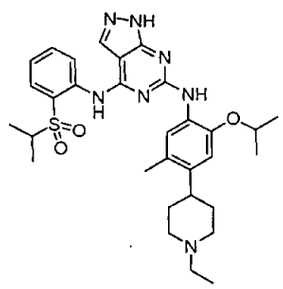
5-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylphenyl)-N-methylpiperidine-2-carboxamide

229



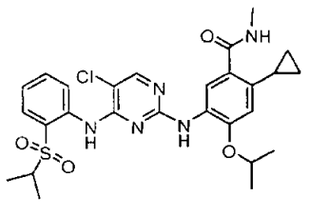
N6-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine

230



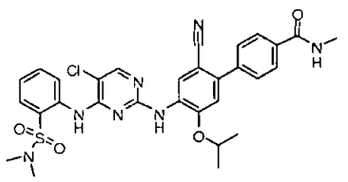
N6-(4-(1-ethylpiperidin-4-yl)-2-isopropoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine

108



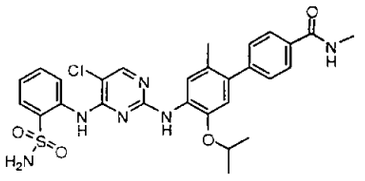
5-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2-cyclopropyl-4-isopropoxy-N-methylbenzamide

109



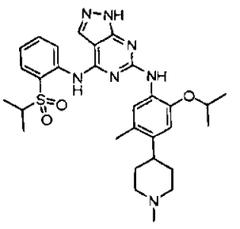
4'-(5-chloro-4-(2-(N,N-dimethylsulfamoyl)phenylamino) pyrimidin-2-ylamino)-2'-cyano-5'-isopropoxy-N-methylbiphenyl-4-carboxamide

110



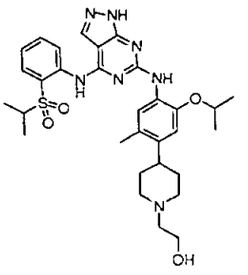
5-chloro-N4-(2-(sulfonylamino)phenyl)-N2-(2-methoxy-5-methyl-4-(3-methyl-4-(methylacetamidophenyl)-phenyl)pyrimidine-2,4-diamine

231



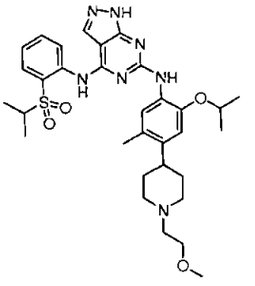
N6-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine

232



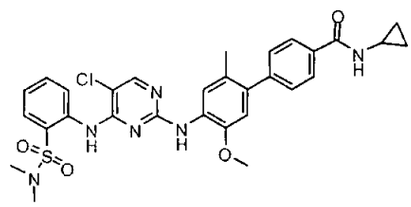
2-(4-(5-isopropoxy-4-(4-(2-(isopropylsulfonyl) phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methylphenyl)piperidin-1-yl)ethanol

233



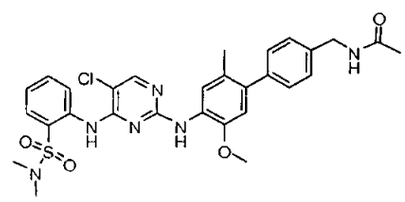
N6-(2-isopropoxy-4-(1-(2-methoxyethyl) piperidin-4-yl)-5-methylphenyl)-N4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine

111



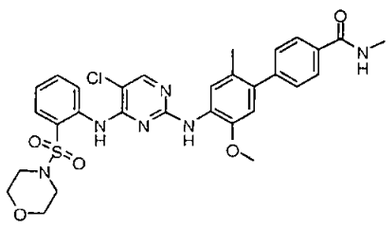
4'-(5-chloro-4-(2-(N,N-dimethylsulfamoyl)phenylamino) pyrimidin-2-ylamino)-N-cyclopropyl-5'-methoxy-2'-methylbiphenyl-4-carboxamide

112



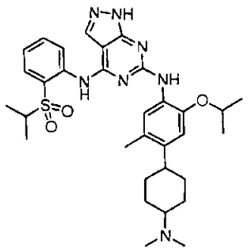
N-((4'-(5-chloro-4-(2-(N,N-dimethylsulfamoyl) phenylamino) pyrimidin-2-ylamino)-5'-methoxy-2'-methylbiphenyl-4-yl)methyl)acetamide

113



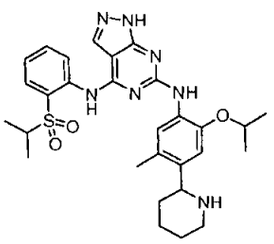
5-chloro-N4-(2-(morpholinosulfonyl) phenyl)-N2-(2-methoxy-5-methyl-4-(4 (methylacetamidophenyl)-phenyl)pyrimidine-2,4-diamine

234



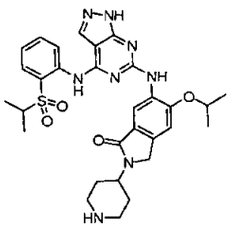
N6-(4-(4-(dimethylamino)cyclohexyl)-2-isopropoxy-5-methylphenyl)-N4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine

235



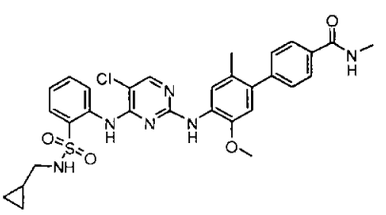
N6-(2-isopropoxy-5-methyl-4-(piperidin-2-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine

236



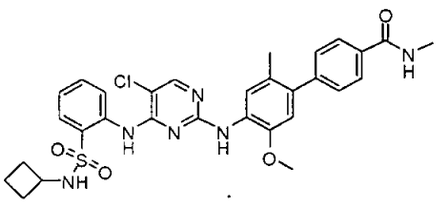
5-isopropoxy-6-(4-(2-(isopropylsulfonyl) phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-(piperidin-4-yl)isoindolin-1-one

114



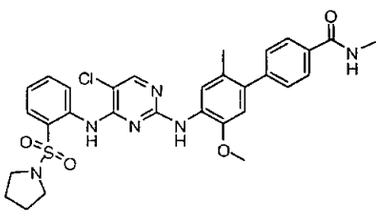
4'-(5-chloro-4-(2-(N-(cyclopropylmethyl) sulfamoyl)phenylamino)pyrimidin-2-ylamino)-5'-methoxy-N,2'-dimethylbiphenyl-4-carboxamide

115



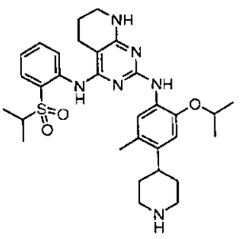
4'-(5-chloro-4-(2-(N-cyclobutyl sulfamoyl)phenylamino)pyrimidin-2-ylamino)-5'-methoxy-N,2'-dimethylbiphenyl-4-carboxamide

116



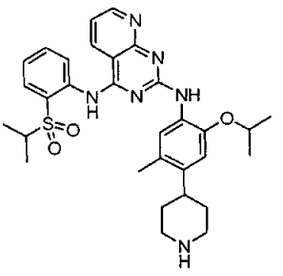
5-chloro-N4-(2-(pyrrolidinosulfonyl) phenyl)-N2-(2-methoxy-5-methyl-4-(4-acetamidomethylphenyl)-phenyl)pyrimidine-2,4-diamine

237



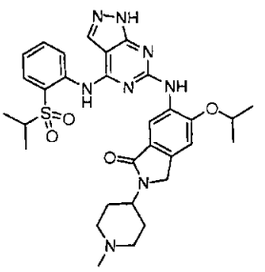
N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine-2,4-diamine

238



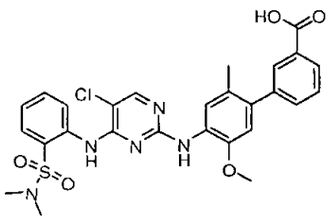
N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrido[2,3-d]pyrimidine-2,4-diamine

239



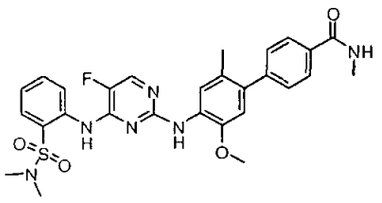
5-isopropoxy-6-(4-(2-(isopropylsulfonyl) phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-(1-methylpiperidin-4-yl)isoindolin-1-one

117



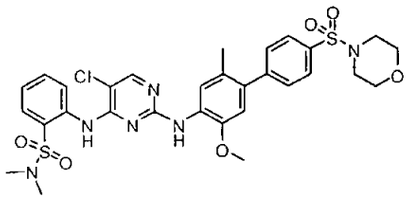
4'-(5-chloro-4-(2-(N,N-dimethylsulfamoyl) phenylamino) pyrimidin-2-ylamino)-5'-methoxy-2'-methylbiphenyl-3-carboxylic acid

118



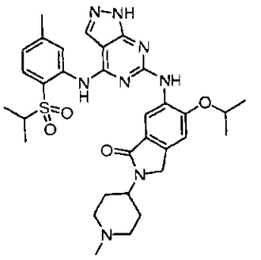
4'-(4-(2-(N,N-dimethylsulfamoyl) phenylamino)-5-fluoropyrimidin-2-ylamino)-5'-methoxy-N,2'-dimethylbiphenyl-4-carboxamide

119



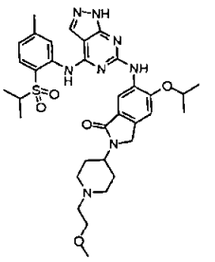
2-(5-chloro-2-(5-methoxy-2-methyl-4'-(morpholinosulfonyl)biphenyl-4-ylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide

240



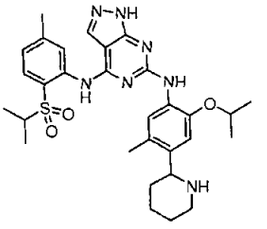
5-isopropoxy-6-(4-(2-(isopropylsulfonyl)-5-methylphenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-(1-methylpiperidin-4-yl)isoindolin-1-one

241



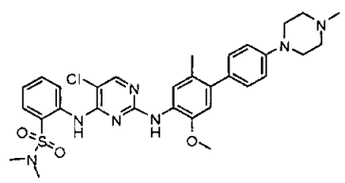
5-isopropoxy-6-(4-(2-(isopropylsulfonyl)-5-methylphenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-(1-(2-methoxy ethyl)piperidin-4-yl)isoindolin-1-one

242



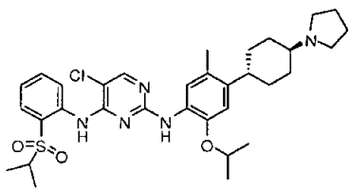
N6-(2-isopropoxy-5-methyl-4-(piperidin-2-yl)phenyl)-N4-(2-(isopropylsulfonyl)-5-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine

120



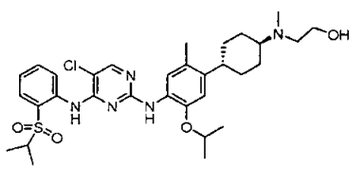
2-(5-chloro-2-(5-methoxy-2-methyl-4'-(4-methylpiperazin-1-yl)biphenyl-4-ylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide

121



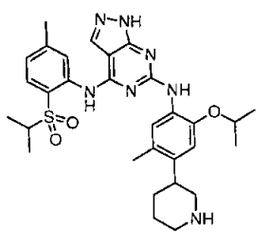
5-chloro-N2-(2-isopropoxy-5-methyl-4-((1r,4r)-4-(pyrrolidin-1-yl)cyclohexyl) phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

122



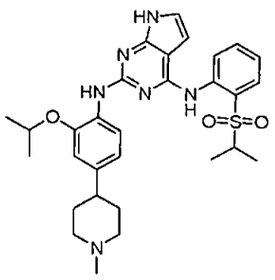
2-(N-((1r,4r)-4-(4-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-5-isopropoxy-2-methylphenyl)cyclohexyl)-N-methylamino)ethanol

243



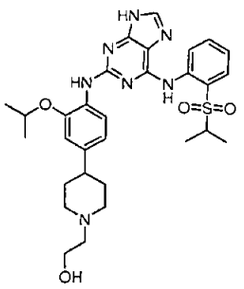
N6-(2-isopropoxy-5-methyl-4-(piperidin-3-yl)phenyl)-N4-(2-(isopropylsulfonyl)-5-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine

244



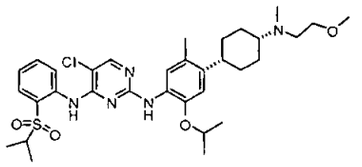
N2-(2-isopropoxy-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

245



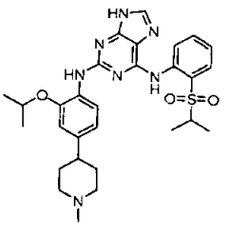
2-(4-(3-isopropoxy-4-(6-(2-(isopropylsulfonyl) phenylamino)-9H-purin-2-ylamino)phenyl)piperidin-1-yl)ethanol; and

123



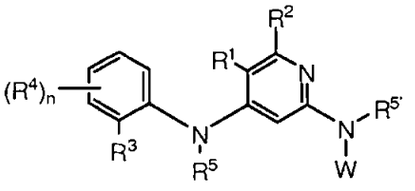
N2-(4-((1s,4s)-4-(N-(2-methoxyethyl)-N-methylamino)cyclohexyl)-2-isopropoxy-5-methylphenyl)-5-chloro-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

246



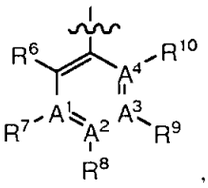
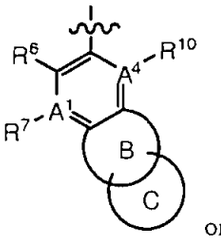
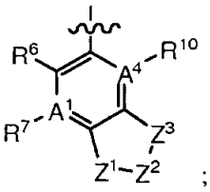
N2-(2-isopropoxy-4-(1-methylpiperidin-4-yl)phenyl)-N6-(2-(isopropylsulfonyl) phenyl)-9H-purine-2,6-diamine.

12. A compound having Formula (5):



(5)

or pharmaceutically acceptable salts thereof; wherein

W is  ,  or  ;

A^1 and A^4 are independently C or N;

each A^2 and A^3 is C, or one of A^2 and A^3 is N when R^6 and R^7 form a ring;

B and C are independently an optionally substituted 5-7 membered carbocyclic ring, aryl, heteroaryl or heterocyclic ring containing N, O or S;

Z^1, Z^2 and Z^3 are independently NR^{11}, C=O, CR-OR, $(CR_2)_{1-2}$ or $=C-R^{12}$;

R^1 and R^2 are independently halo, OR^{12}, $NR(R^{12})$, SR^{12}, or an optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; or one of R^1 and R^2 is H;

R^3 is $(CR_2)_{0-2}SO_2R^{12}$, $(CR_2)_{0-2}SO_2NRR^{12}$, $(CR_2)_{0-2}CO_{1-2}R^{12}$, $(CR_2)_{0-2}CONRR^{12}$ or cyano;

R^4, R^6, and R^7 and R^{10} when attached to a carbon atom, are independently H, an optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; OR^{12}, $NR(R^{12})$, halo, nitro, SO_2R^{12}, $(CR_2)_pR^{13}$ or X; provided R^6 and R^7 are not both H;

R, R^5 and $R^{5'}$ are independently H or C_{1-6} alkyl;

R^8 and R^9 are independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo or X, or one of R^8 and R^9 is H; and provided one of R^8 and R^9 is X;

alternatively, R^1 and R^2, or R^6 and R^7, R^7 and R^8, or R^9 and R^{10}, when attached to a carbon atom may form an optionally substituted 5-7 membered monocyclic or fused carbocyclic ring, aryl, or heteroaryl or heterocyclic ring comprising N, O and/or S; or R^7, R^8, R^9 and R^{10} are absent when attached to N;

R^{11} is H, C_{1-6} alkyl, C_{2-6} alkenyl, $(CR_2)_pCO_{1-2}R$, $(CR_2)_pOR$, $(CR_2)_pR^{13}$, $(CR_2)_pNRR^{12}$, $(CR_2)_pCONRR^{12}$ or $(CR_2)_pSO_{1-2}R^{12}$;

R^{12} and R^{13} are independently an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, or a 5-7 membered heterocyclic ring comprising N, O and/or S; aryl or heteroaryl; or R^{12} is H, C_{1-6} alkyl;

X is $(CR_2)_qY$, cyano, $CO_{1-2}R^{12}$, $CONR(R^{12})$, $CONR(CR_2)_pNR(R^{12})$, $CONR(CR_2)_pOR^{12}$, $CONR(CR_2)_pSR^{12}$, $CONR(CR_2)_pS(O)_{1-2}R^{12}$ or $(CR_2)_{1-6}NR(CR_2)_pOR^{12}$;

Y is an optionally substituted 3-12 membered carbocyclic ring, a 5-12 membered aryl, or a 5-12 membered heteroaryl or heterocyclic ring comprising N, O and/or S and attached to A^2 or A^3 or both via a carbon atom of said heteroaryl or heterocyclic ring when q in $(CR_2)_qY$ is 0; and

n, p and q are independently 0-4.

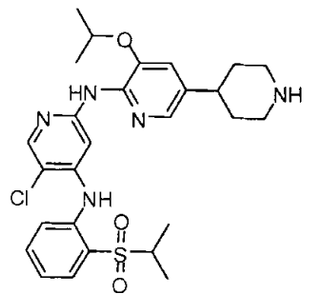
13. The compound of claim 12, wherein R^1 is halo or C_{1-6} alkyl;

R^2 is H or NH_2; or

R^1 and R^2 together form an optionally substituted 5-6 membered aryl, or heteroaryl or heterocyclic ring comprising 1-3 nitrogen atoms.

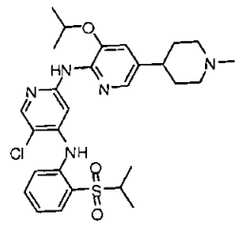
14. The compound of claim 12, selected from the group consisting of

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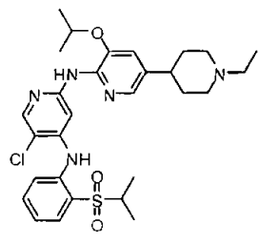
5-chloro-N2-(3-isopropoxy-5-(piperidin-4-yl)pyridin-2-yl)-N4-(2-(isopropylsulfonyl) phenyl)pyridine-2,4-diamine

248



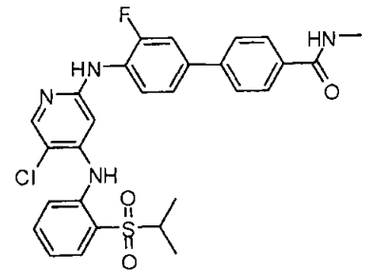
5-chloro-N2-(3-isopropoxy-5-(1-methylpiperidin-4-yl)pyridin-2-yl)-N4-(2-(isopropylsulfonyl) phenyl)pyridine-2,4-diamine

249



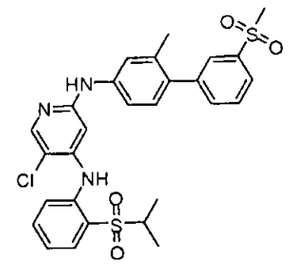
5-chloro-N2-(5-(1-ethylpiperidin-4-yl)-3-isopropoxypyridin-2-yl)-N4-(2-(isopropylsulfonyl) phenyl)pyridine-2.4-diamine

252



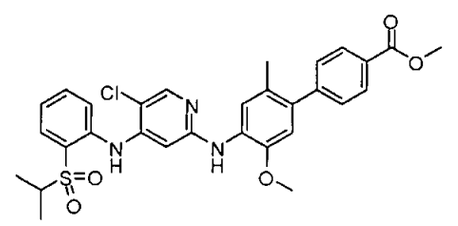
4'-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino) pyridin-2-ylamino)-3'-fluoro-N-methylbiphenyl-4-carboxamide

253



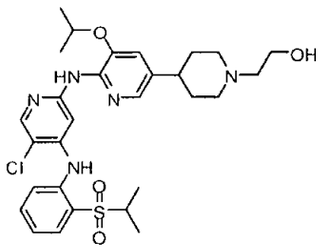
5-chloro-N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methyl-3'-(methylsulfonyl)biphenyl-4-yl)pyridine-2,4-diamine

254



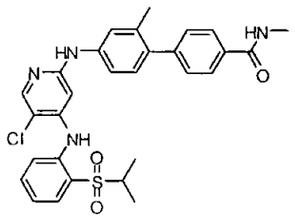
Methyl 4'-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino)pyridin-2-ylamino)-5'-methoxy-2'-methylbiphenyl-4-carboxylate

250



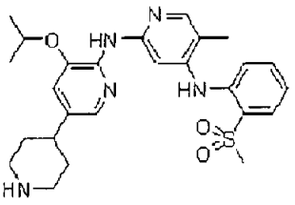
2-(4-(6-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino)pyridin-2-ylamino)-5-isopropoxypyridin-3-yl)piperidin-1-yl)ethanol

251



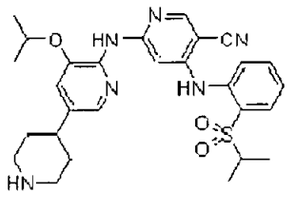
4'-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino) pyridin-2-ylamino)-N,2'-dimethylbiphenyl-4-carboxamide

255



N2-(3-isopropoxy-5-(piperidin-4-yl)pyridin-2-yl)-5-methyl-N4-(2-(methylsulfonyl)phenyl)pyridine-2,4-diamine; and

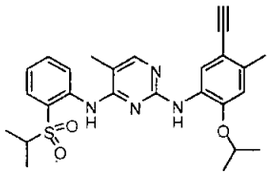
256



6-(3-isopropoxy-5-(piperidin-4-yl)pyridin-2-ylamino)-4-(2-(isopropylsulfonyl) phenylamino) nicotinonitrile.

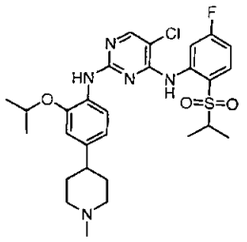
15. A compound selected from the group consisting of

257



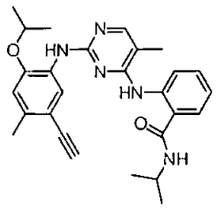
N2-(5-Ethynyl-2-isopropoxy-4-methyl-phenyl)-5-methyl-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine

274



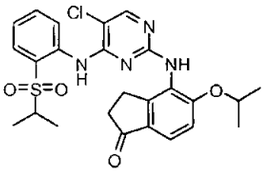
5-chloro-N4-(5-fluoro-2-(isopropylsulfonyl) phenyl)-N2-(2-isopropoxy-4-(1-methyl piperidin-4-yl)phenyl)pyrimidine-2,4-diamine

258



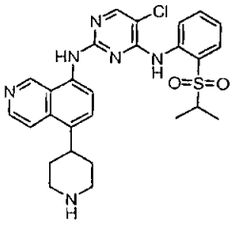
2-(2-(5-ethynyl-2-isopropoxy-4-methylphenylamino)-5-methylpyrimidin-4-ylamino)-N-isopropylbenzamide

259



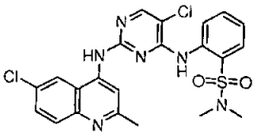
4-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-2,3-dihydro-5-isopropoxyinden-1-one

260



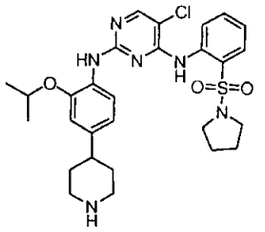
5-chloro-N4-(2-(isopropylsulfonyl) phenyl)-N2-(5-(piperidin-4-yl)isoquinolin-8-yl)pyrimidine-2,4-diamine

261



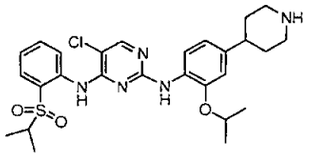
2-[5-Chloro-2-(6-chloro-2-methyl-quinolin-4-ylamino)-pyrimidin-4-ylamino]-N,N-dimethyl-benzenesulfonamide

275



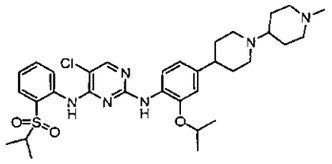
5-chloro-N2-(2-isopropoxy-4-(piperidin-4-yl)phenyl)-N4-(2-(pyrrolidin-1-ylsulfonyl)phenyl)pyrimidine-2,4-diamine

276



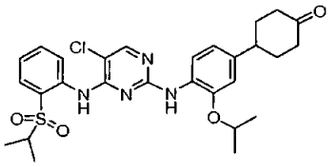
5-chloro-N2-(2-isopropoxy-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

277



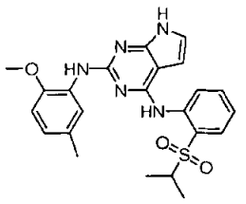
5-chloro-N2-(2-isopropoxy-4-(1-(1-methylpiperidin-4-yl)piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

278



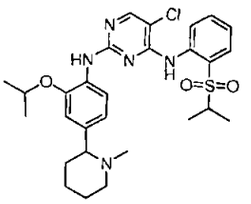
4-(4-(4-(2-(isopropylsulfonyl)phenylamino)-5-chloropyrimidin-2-ylamino)-3-isopropoxyphenyl)cyclohexanone

262



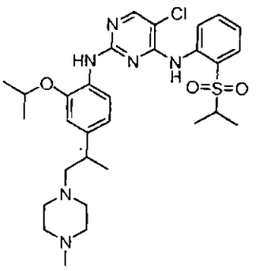
N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methoxy-5-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

263



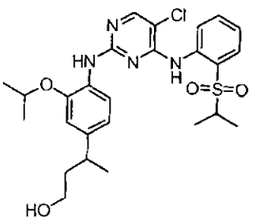
5-chloro-N2-(2-isopropoxy-4-(1-methyl piperidin-2-yl)phenyl)-N4-(2-(isopropyl sulfonyl)phenyl)pyrimidine-2,4-diamine

264



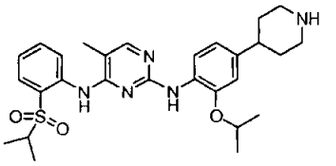
5-chloro-N2-(2-isopropoxy-4-(1-(4-methylpiperazin-1-yl)propan-2-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl) pyrimidine-2,4-diamine

265



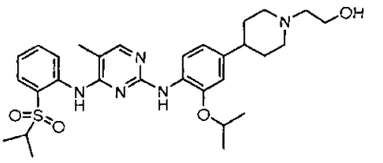
3-(4-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino) pyrimidin-2-ylamino)-3-isopropoxyphenyl)butan-1-ol

279



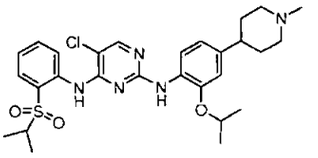
N2-(2-isopropoxy-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine

280



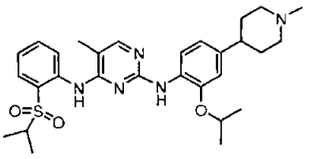
2-(4-(4-(4-(2-(isopropylsulfonyl)phenylamino)-5-methylpyrimidin-2-ylamino)-3-isopropoxy phenyl)piperidin-1-yl)ethanol

281



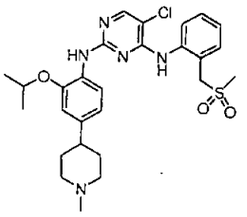
5-chloro-N2-(2-isopropoxy-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine

282



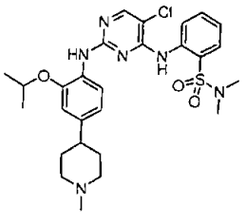
N2-(2-isopropoxy-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)-5-methylpyrimidine-2,4-diamine

266



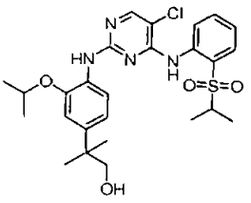
5-chloro-N2-(2-isopropoxy-4-(1-methylpiperidin-4-yl)phenyl)-N4-(2-(methylsulfonylmethyl) phenyl)pyrimidine-2,4-diamine

267



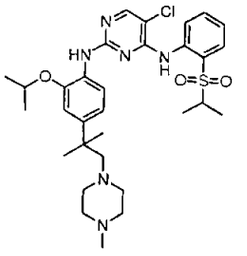
2-(5-chloro-2-(2-isopropoxy-4-(1-methyl piperidin-4-yl)phenylamino) pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide

268



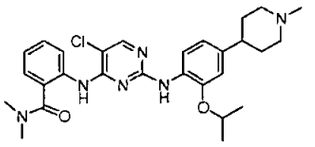
2-(4-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino) pyrimidin-2-ylamino)-3-isopropoxyphenyl)-2-methylpropan-1-ol

269



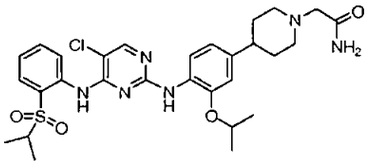
5-chloro-N2-(2-isopropoxy-4-(2-methyl-1-(4-methylpiperazin-1-yl)propan-2-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

283



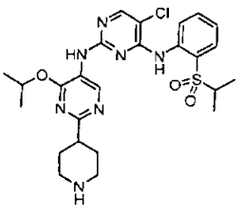
2-(2-(2-isopropoxy-4-(1-methylpiperidin-4-yl)phenylamino)-5-chloropyrimidin-4-ylamino)-N,N-dimethylbenzamide

284



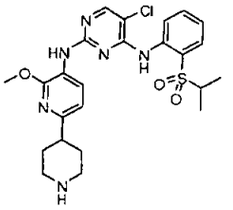
2-(4-(4-(4-(2-(isopropylsulfonyl) phenylamino)-5-chloropyrimidin-2-ylamino)-3-isopropoxyphenyl) piperidin-1-yl)acetamide

285



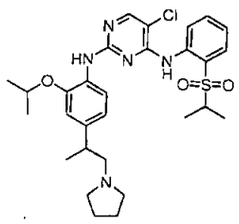
5-chloro-N2-(4-isopropoxy-2-(piperidin-4-yl)pyrimidin-5-yl)-N4-(2-(isopropyl sulfonyl)phenyl)pyrimidine-2,4-diamine

286



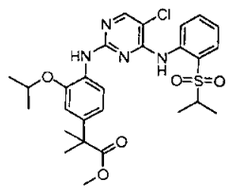
5-chloro-N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methoxy-6-(piperidin-4-yl)pyridin-3-yl) pyrimidine-2,4-diamine

270



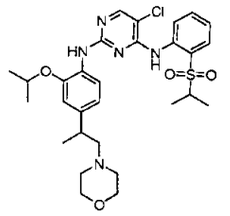
5-chloro-N2-(2-isopropoxy-4-(1-(pyrrolidin-1-yl)propan-2-yl)phenyl)-N4-(2-(isopropylsulfonyl) phenyl)pyrimidine-2,4-diamine

271



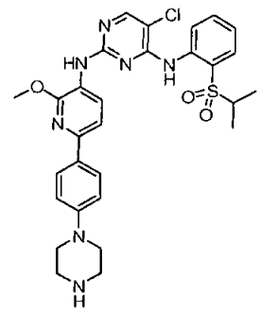
Methyl 2-(4-(5-chloro-4-(2-(isopropylsulfonyl) phenylamino)pyrimidin-2-ylamino)-3-isopropoxyphenyl)-2-methylpropanoate

272



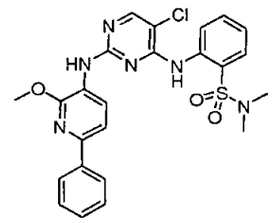
5-chloro-N2-(2-isopropoxy-4-(1-morpholinopropan-2-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine

287



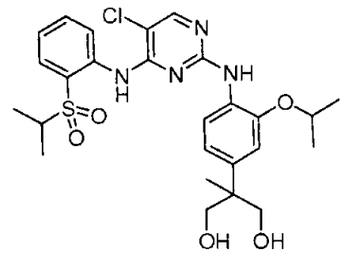
5-chloro-N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methoxy-6-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)pyrimidine-2,4-diamine

288



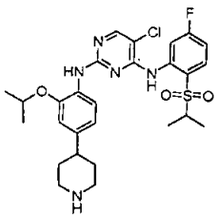
2-(5-chloro-2-(2-methoxy-6-phenylpyridin-3-ylamino)pyrimidin-4-ylamino)-N,N-dimethylbenzenesulfonamide; and

289



2-(4-(5-chloro-4-(2-(isopropylsulfonyl)phenylamino) pyrimidin-2-ylamino)-3-isopropoxyphenyl)-2-methylpropane-1,3-diol.

273



5-chloro-N4-(5-fluoro-2-(isopropylsulfonyl)phenyl)-N2-(2-isopropoxy-4-(piperidin-4-yl)phenyl)pyrimidine-2,4-diamine

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1-15 and a pharmaceutically acceptable carrier.

17. A method for inhibiting anaplastic lymphoma kinase, comprising administering to a cell or tissue system or to a mammalian subject, a therapeutically effective amount of a compound of any one of claims 1-15, or pharmaceutically acceptable salts thereof, thereby inhibiting said kinase.

18. The use of a compound of any one of claims 1-15, or a pharmaceutical composition thereof, for the manufacture of a medicament for treating a condition mediated by anaplastic lymphoma kinase, and optionally in combination with a second therapeutic agent, wherein said condition is an autoimmune disease, a transplantation disease, an infectious disease or a cell proliferative disorder.

19. The use of a compound of any one of claims 1-15, or a pharmaceutical composition thereof, for the manufacture of a medicament for treating a cell proliferative disorder, and optionally in combination with a second therapeutic agent, wherein said cell proliferative disorder is lymphoma, osteosarcoma, melanoma, or a tumor of breast, renal, prostate, colorectal, thyroid, ovarian, pancreatic, neuronal, lung, uterine or gastrointestinal tumor.

20. The use of claim 19, wherein said second therapeutic agent is a chemotherapeutic agent.

COMPUESTOS Y COMPOSICIONES COMO INHIBIDORES DE LA PROTEÍNA QUINASA

Referencia cruzada a solicitudes relacionadas

[0001] Esta solicitud reclama beneficio de la solicitud provisional EE.UU. de serie. 60/869, 299, presentada el 8 de diciembre de 2006, que es incorporada en su totalidad por referencia en este documento.

Campo Técnico

[0002] La invención se refiere a los inhibidores de la proteína quinasa, en particular los nuevos derivados de piridina y pirimidina y composiciones farmacéuticas, y su uso como productos farmacéuticos.

Antecedentes

[0003] El linfoma anaplásico de quinasa (ALK), miembro de la superfamilia de los receptores de insulina de los receptores de tirosina quinasas, se ha implicado en la oncogénesis en tumores hematopoyéticos y no hematopoyéticos. La expresión aberrante de las proteínas completas del receptor ALK ha sido reportado en neuroblastomas y glioblastomas, y proteínas ALK de fusión se han producido en el linfoma anaplásico de células grandes. El estudio de las proteínas de fusión ALK ha planteado también la posibilidad de nuevos tratamientos terapéuticos para pacientes con neoplasias ALK-positivos. (Pulford et al. Cell. Mol. Life Sci.. 61:2939-2953 (2004)).

[0004] La quinasa de adición focal (FAK) es una enzima clave en la integrina mediada fuera en la señal de cascada (D. Schlaepfer et al. Prog Biophys Mol Biol 1999, 71, 43578). El disparador en la señal de la cascada de transducción es la autofosforilación de Y397. La Y397 fosforilada es un sitio de acoplamiento SH2 para la familia Src de tirosina quinasas, la unión c-Src tirosina quinasa fosforila otros residuos en FAK. Entre ellos, la Y925 fosforilada se convierte en un sitio de unión para el sitio SH2 de la proteína adaptadora pequeña de Grb2. La unión directa de Grb2 a FAK es uno de los pasos clave para la activación de objetivos tales como la cascada quinasa Ras-ERK2/MAP.

[0005] La proteína quinasa 70 (ZAP-70) asociada a la cadena Zeta, miembro de la familia de la proteína tirosina quinasa, es de importancia potencial en el pronóstico de la leucemia linfocítica crónica (LLC). La ZAP-70 se sabe que es de importancia en la señalización celular de los linfocitos T y NK, pero ausente en células B periféricas normales, se expresa en la mayoría de los pronósticos más pobres de LLC no mutados y ausente en la mayoría de los casos con los

genes mutados IgVH. La ZAP-70 se expresa también en una minoría de otros tumores de células B. (Orchard et al. Leuk. Linfoma 46:1689-98 (2005)).

[0006]

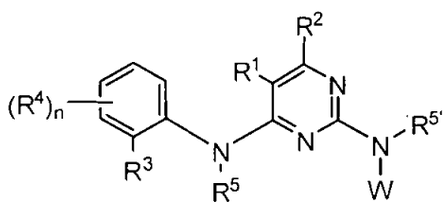
El factor de crecimiento similar a insulína (IGF-1) la señalización está altamente implicada en el cáncer, con el receptor IGF-1 (IGF-1R) como el factor predominante. IGR-1R es importante para la transformación tumoral y la supervivencia de las células malignas, pero es sólo en parte normal de las células que participan en el crecimiento. Apuntar a IGF-1R se ha sugerido como una opción prometedora para la terapia del cáncer. (Larsson et al., Fr. J. Cancer 92:2097-2101 (2005)).

[0007] Debido a las enfermedades emergentes relacionadas con las funciones de ALK, FAK, ZAP-70 y el IGF-1R, existe una continua necesidad de compuestos que pueden ser útiles para el tratamiento y la prevención de enfermedades que responden a la inhibición de ALK, FAK, ZAP-70 y / o IGF-1R.

Revelación de la invención

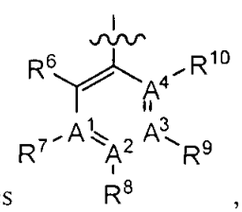
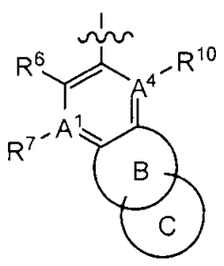
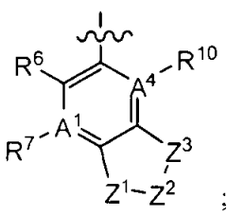
[0008] Esta invención se relaciona con nuevos derivados de pirimidina y piridina y composiciones farmacéuticas de los mismos, y su uso en farmacia.

[0009] En a unapecto, la invención proporcionada tiene la Fórmula (1):



(I)

o sales farmacéuticamente aceptables del mismo; donde

W es  ,  or  ;

A^1 y A^4 son independientemente C o N;

cada A^2 y A^3 es C, o uno de A^2 y A^3 es N donde R^6 y R^7 forman un anillo;

B y C son independientemente un anillo carbocíclico de 5-7 miembros opcionalmente sustituido, aril, heteroaril o un anillo heterocíclico que contiene N, O o S;

Z^1, Z^2 y Z^3 son independientemente NR^{11}, C=O, CR-OR, $(CR_2)_{1-2}$ o =C-R^{12};

R^1 y R^2 son independientemente halo, OR^{12}, $NR(R^{12})$, SR^{12}, o un C_{1-6} alquil, C_{2-6} alquenil o C_{2-6} alquinil, opcionalmente sustituidos; o uno de R^1 y R^2 es H;

R^3 es $(CR_2)_{0-2}SO_2R^{12}$, $(CR_2)_{0-2}SO_2NRR^{12}$, $(CR_2)_{0-2}CO_{1-2}R^{12}$, $(CR_2)_{0-2}CONRR^{12}$ o ciano;

R^4, R^6, R^7 y R^{10} son independientemente un C_{1-6} alquil, C_{2-6} alquenil o C_{2-6} alquinil, opcionalmente sustituidos; OR^{12}, $NR(R^{12})$, halo, nitro, SO_2R^{12}, $(CR_2)_pR^{13}$ o X; o R^4, R^7 y R^{10} son independientemente H;

R, R^5 y $R^{5'}$ son independientemente H o C_{1-6} alquil;

R^8 y R^9 son independientemente C_{1-6} alquil, C_{2-6} alquenil, C_{2-6} alquinil, halo o X, o uno de R^8 y R^9 es H donde R^1 y R^2 forman un anillo; y siempre que uno de R^8 y R^9 sea X;

alternativamente, R^1 y R^2, o R^6 y R^7, R^7 y R^8, o R^9 y R^{10}, donde estén unidos un un átomo de carbono, pueden formar un anillo monocíclico o fusionado de 5-7 miembros carbocíclico, arílico, o heteroarílico opcionalmente sustituido o un anillo heterocíclico que comprende N, O o ; o R^7, R^8, R^9 y R^{10} están ausentes cuyo están unidos a un N;

R^{11} es H, C_{1-6} alquil, C_{2-6} alquenil, $(CR_2)_pCO_{1-2}R$, $(CR_2)_pOR$, $(CR_2)_pR^{13}$, $(CR_2)_pNRR^{12}$, $(CR_2)_pCONRR^{12}$ o $(CR_2)_pSO_{1-2}R^{12}$;

R^{12} y R^{13} son independientemente un anillo carbocíclico de 3-7 miembros saturado o parcialmente insaturado opcionalmente sustituido, o un anillo heterocíclico de 5-7 miembros que comprende N, O y/o S; aril o heteroaril; o R^{12} es H, C_{1-6} alquil;

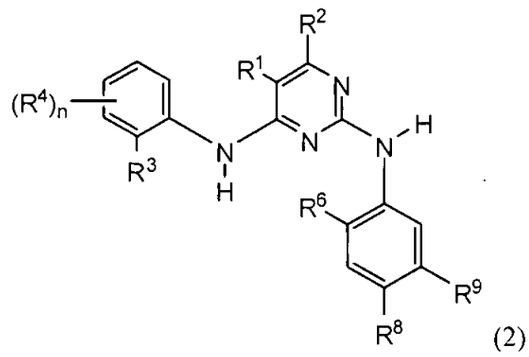
X es $(CR_2)_qY$, ciano, $CO_{1-2}R^{12}$, $CONR(R^{12})$, $CONR(CR_2)_pNR(R^{12})$, $CONR(CR_2)_pOR^{12}$, $CONR(CR_2)_pSR^{12}$, $CONR(CR_2)_pS(O)_{1-2}R^{12}$ o $(CR_2)_{1-6}NR(CR_2)_pOR^{12}$;

Y es un anillo carbocíclico de 3-12 miembros opcionalmente sustituido, un aril de 5-12 miembros, o un anillo heteroaril de 5-12 miembros o heterocíclico que comprende N, O y/o S y unidos a a un^2 o A^3 o ambos por medio de un átomo de carbono de dicho heteroaril o un anillo heterocíclico donde q en $(CR_2)_qY$ es 0; y

n, p y q son independientemente 0-4.

|0010| En la anterior Fórmula (1), R^1 puede ser halo o C_{1-6} alquil; R^2 es H o NH_2; o R^1 y R^2 juntos forman un anillo de 5-6 miembros arílico, o heteroarílico o heterocíclico opcionalmente sustituido que comprende 1-3 átomos de nitrógeno. En otros ejemplos, R^3 en la Fórmula (1) puede ser SO_2R^{12}, SO_2NH_2, SO_2NRR^{12}, CO_2NH_2, $CONRR^{12}$, $CO_{1-2}R^{12}$, o ciano; y R^{12} es C_{1-6} alquil, un C_{3-7} cicloalquil, C_{3-7} cicloalquenil, pirrolidinil, piperazinil, piperidinil, morfolinil o azetidinil, opcionalmente sustituidos. Aún en otros ejemplos, R^5, $R^{5'}$, R^7 y R^{10} en la Fórmula (1) son independientemente H, y n es 0. En otros ejemplos, R^6 en la Fórmula (1) puede ser halo o OR^{12}, y R^{12} es C_{1-6} alquil.

[0011] En una modalidad, la invención proporciona un compuestos que tienen la Fórmula (2):



(2)

donde R^1 es halo o C_{1-6} alquil;

R^2 es H; o

R^1 y R^2 juntos forman un anillo heteroarilo o heterocíclico de 5-6 miembros opcionalmente sustituido que comprende uno o dos átomos de nitrógeno;

R^6 es isopropoxi o metoxi;

uno de R^8 y R^9 es $(CR_2)_qY$ y el otro es C_{1-6} alquil, ciano, $CO_{1-2}R^{12}$, $CONR(R^{12})$ o $CONR(CR_2)_pNR(R^{12})$;

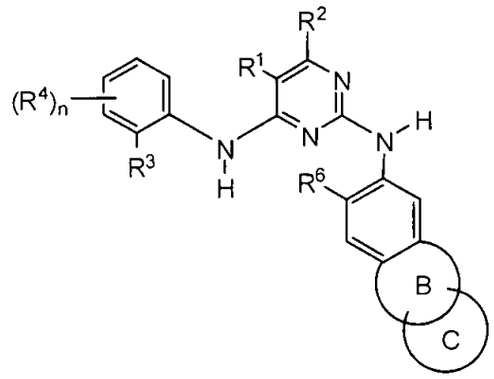
Y es un C_{3-7} cicloalquil, C_{3-7} cicloalquenil, o fenil, opcionalmente sustituidos; o Y es piridil, pirazolil, isoxazolil, imidazolil, tiazolil, benzimidazolil, pirrolidinil, piperazinil, piperidinil, morfolinil, azetidinil, heptametileneimina o octametileneimina, cada uno de los cuales están unidos al anillo fenil por medio de un átomo de carbono donde q en $(CR_2)_qY$ es 0;

n es 0-1; y

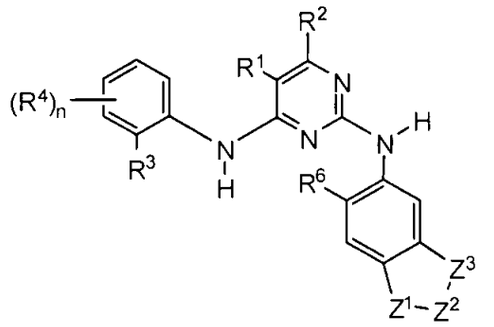
q es 0-4.

[0012] En la anterior Fórmula (2), uno de R^8 y R^9 puede ser $(CR_2)_qY$ y el otro es C_{1-6} alquil; y n y q son independientemente 0. En algunos ejemplos, Y es pirrolidinil, piperidinil, azetidinil. En otros ejemplos, R^1 es halo o C_{1-6} alquil; y R^2 es H.

[0013] En otra modalidad, la invención proporciona un compuesto que tienen la Fórmula (3A) o (3B):

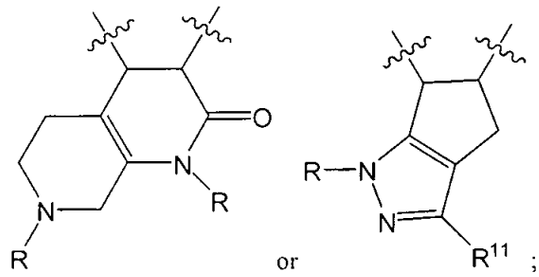


(3A)



(3B)

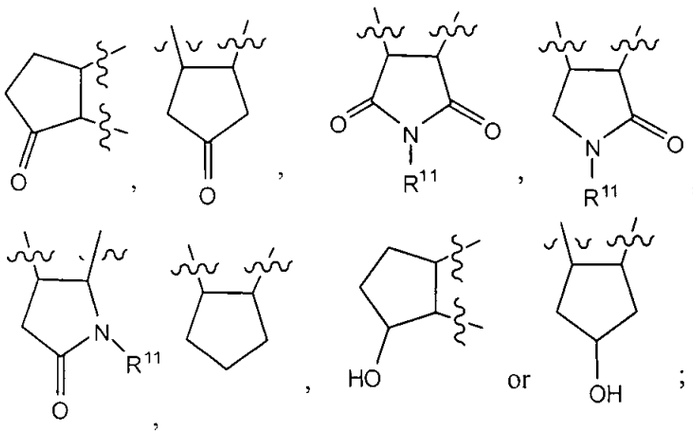
donde B y C juntos forman



or

;

Z^1, Z^2 y Z^3 juntos forman



o tautómeros de los mismos;

R^1 es halo o C_{1-6} alquil;

R^2 es H; o

R^1 y R^2 juntos forman un anillo carbocíclico de 5-7 miembros opcionalmente sustituido, aril, o heteroaril o un anillo heterocíclico que comprende N, O y/o S; y

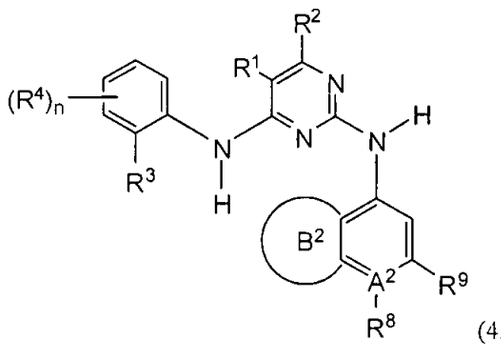
R^6 es isopropoxi o metoxi.

[0014] En la anterior Fórmula (3A) o (3B), cada R^{11} puede ser $(CR_2)_pCO_{1-2}R$, $(CR_2)_pOR$, $(CR_2)_pR^{13}$, $(CR_2)_pNRR^{12}$ o $(CR_2)_pCONRR^{12}$;

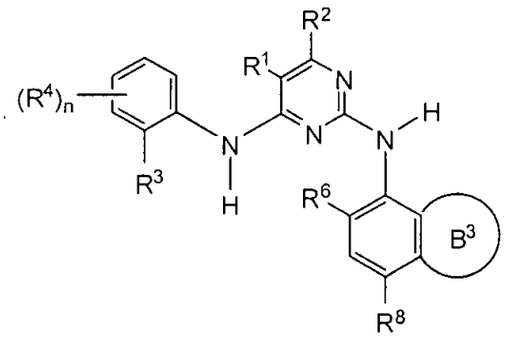
R y R^{12} son independientemente H o C_{1-6} alquil; y

R^{13} es un piperidinil, azetidiil, tetrahidropiranil, ciclohexil, morfolinil, pirrolidinil, heptametileneimina, octametileneimina, un derivado de amina bicíclica o diamina, quinuclidin-3-il, 8-metil-8-aza-biciclo[3.2.1]oct-6-il], o 9-metil-9-aza-biciclo[4.2.1]nonan-7-il, opcionalmente sustituidos.

[0015] Aún en otra modalidad, la invención proporciona un compuestos que tienen la Fórmula (4A) o Fórmula (4B):



(4A)



(4B);

donde R^1 es halo o C_{1-6} alquil;

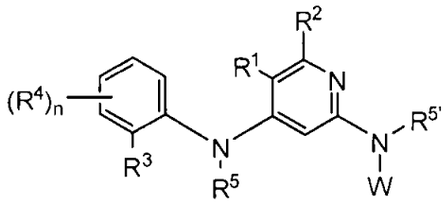
R^2 es H; o

R^1 y R^2 juntos forman un anillo carbocíclico de 5-7 miembros opcionalmente sustituido, aril, o heteroaril o un anillo heterocíclico que comprende N, O y/o S;

R^6 es isopropoxi o metoxi; y

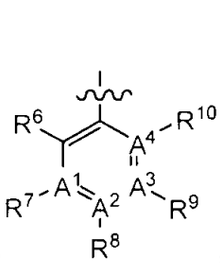
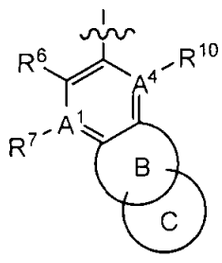
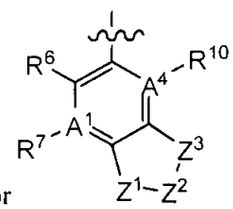
B^2 y B^3 son independientemente un aril de 5-6 miembros opcionalmente sustituido o heteroaril que contiene N, O o S.

[0016] En otro aspecto, la invención proporciona un compuestos que tienen la Fórmula (5):



(5)

o sales farmacéuticamente aceptables del mismo; donde

W es  ,  or  ;

A^1 y A^4 son independientemente C o N;

cada A^2 y A^3 es C, o uno de A^2 y A^3 es N donde R^6 y R^7 forman un anillo;

B y C son independientemente un anillo carbocíclico de 5-7 miembros opcionalmente sustituido, aril, heteroaril o un anillo heterocíclico que contiene N, O o S;

Z^1, Z^2 y Z^3 son independientemente NR^{11}, C=O, CR-OR, $(CR_2)_{1-2}$ o =C-R^{12};

R^1 y R^2 son independientemente halo, OR^{12}, $NR(R^{12})$, SR^{12}, o un C_{1-6} alquil, C_{2-6} alquenil o C_{2-6} alquinil, opcionalmente sustituidos; o uno de R^1 y R^2 es H;

R^3 es $(CR_2)_{0-2}SO_2R^{12}$, $(CR_2)_{0-2}SO_2NRR^{12}$, $(CR_2)_{0-2}CO_{1-2}R^{12}$, $(CR_2)_{0-2}CONRR^{12}$ o ciano;

R^4, R^6, y R^7 y R^{10} cuyo están unidos a un átomo de carbono, son independientemente H, un C_{1-6} alquil, C_{2-6} alquenil o C_{2-6} alquinil, opcionalmente sustituidos; OR^{12}, $NR(R^{12})$, halo, nitro, SO_2R^{12}, $(CR_2)_pR^{13}$ o X; siempre que R^6 y R^7 no son ambos H;

R, R^5 y $R^{5'}$ son independientemente H o C_{1-6} alquil;

R^8 y R^9 son independientemente C_{1-6} alquil, C_{2-6} alquenil, C_{2-6} alquinil, halo o X, o uno de R^8 y R^9 es H; y siempre que uno de R^8 y R^9 es X;

alternativamente, R^1 y R^2, o R^6 y R^7, R^7 y R^8, o R^9 y R^{10}, cuyo están unidos a un átomo de carbono pueden formar un anillo carbocíclico monocíclico o fusionado de 5-7 miembros opcionalmente sustituido, aril, o heteroaril o un anillo heterocíclico que comprende N, O y/o S; o R^7, R^8, R^9 y R^{10} están ausentes cuyo están unidos a un N;

R^{11} es H, C_{1-6} alquil, C_{2-6} alquenil, $(CR_2)_pCO_{1-2}R$, $(CR_2)_pOR$, $(CR_2)_pR^{13}$, $(CR_2)_pNRR^{12}$, $(CR_2)_pCONRR^{12}$ o $(CR_2)_pSO_{1-2}R^{12}$;

R^{12} y R^{13} son independientemente un anillo carbocíclico de 3-7 miembros saturado o parcialmente insaturado opcionalmente sustituido, o un anillo heterocíclico de 5-7 miembros que comprende N, O y/o S; aril o heteroaril; o R^{12} es H, C_{1-6} alquil;

X es $(CR_2)_qY$, ciano, $CO_{1-2}R^{12}$, $CONR(R^{12})$, $CONR(CR_2)_pNR(R^{12})$, $CONR(CR_2)_pOR^{12}$, $CONR(CR_2)_pSR^{12}$, $CONR(CR_2)_pS(O)_{1-2}R^{12}$ o $(CR_2)_{1-6}NR(CR_2)_pOR^{12}$;

Y es un anillo carbocíclico de 3-12 miembros opcionalmente sustituido, un aril de 5-12 miembros, o un heteroaril de 5-12 miembros o un zanillo heterocíclico que comprende N, O y/o S y unidos a a un[2] o A^3 o ambos por medio de un átomo de carbono de dicho heteroaril o un anillo heterocíclico donde q en $(CR_2)_qY$ es 0; y

n, p y q son independientemente 0-4.

[0017] Aún en otro aspecto, la presente invención proporciona composiciones farmacéuticas que comprenden Un compuesto que tiene la Fórmula (1), (2), (3A), (3B), (4A), (4B) o (5), y un excipiente farmacéuticamente aceptable.

[0018] Aún en otro aspecto, la invención proporciona métodos para modular ALK, FAK, ZAP-70 y/o IGF-1R, que comprenden administrar a un sistem o un sujeto con la necesidad, una cantidad terapéuticamente efectiva de un compuesto que tiene la Fórmula (1), (2), (3A), (3B), (4A), (4B) o (5), o sales farmacéuticamente aceptables o composiciones farmacéuticas de los mimos, así modulyo dichos ALK, FAK, ZAP-70 y/o IGF-1R. La invención también proporciona métodos para tratar, mejorar o prevenir una condición que responda a la inhibición de ALK, FAK, ZAP-70 y/o IGF-1R, que comprende la administración a un sistema o a un sujeto que necesitan ese tratamiena una cantidad efectiva de un compuesto que tiene la Fórmula (1), (2), (3A), (3B), (4), (4B) o (5), o sales farmacéuticamente aceptables o composiciones farmacéuticas, y opcionalmente en combinación con un segundo agente terapéutico, así para el tratamiento de dicha condición. Como alternativa, la presente invención proporciona el uso de un compuesto que tiene la Fórmula (1), (2), (3A), (3B), (4), (4B) o (5) en la fabricación de un medicamento para el tratamiento de una condición mediada por ALK, FAK, ZAP-70 y / o IGF-1R. En particular, las modalidades de los compuestos de la invención puede ser utilizado solos o en combinación con un segundo agente terapéutico para el tratamiento de una enfermedad mediada por ALK, donde dicha condición es una enfermedad autoinmune, una enfermedad por etrasplante, una enfermedad infecciosa o un trastorno de proliferación celular.

[0019]

Además, la invención proporciona métodos para el tratamiento de un trastorno de proliferación celular, que comprende la administración a un sistema o un sujeto que necesita ese tratamiento una cantidad efectiva de un compuesto que tiene la Fórmula (1), (2), (3A), (3B), (4), (4B) o (5), o sales farmacéuticamente aceptables o composiciones farmacéuticas, y opcionalmente en combinación con un segundo agente terapéutico, así, para el tratamiento de dicha condición. Como alternativa, la presente invención proporciona el uso de un compuesto que tiene la Fórmula (1), (2), (3A), (3B), (4), (4B) o (5) en la fabricación de un medicamento para el tratamiento de un trastorno proliferativo celular. En ejemplos particulares, los compuestos de la invención pueden ser utilizados solos o en combinación con un agente de quimioterapia para tratar un trastorno de proliferación celular, incluyendo pero no limitado al linfoma, osteosarcoma, melanoma, o un tumor de mama, renal, de próstata, colorrectal , tiroides, ovario, páncreas, neuronal, de pulmón, de útero o tumor gastrointestinal.

[0020] En los métodos anteriores para el uso de los compuestos de la invención, un compuesto que tenga la fórmula (1), (2), (3A), (3B), (4), (4B) o (5) puede ser administrado a un sistema de células o tejidos, o a un mamífero tal como un sujeto humano o un sujeto animal.

Definiciones

[0021] "Alquil" se refiere a un grupo y como un elemento estructura a otros grupos, por ejemplo alquil-sustituido por-halo y alcoxi, y puede ser de cadena recta o ramificada. A unlquil, alquenil o alquinil, opcionalmente sustituidos, como se usa aquí puede estar opcionalmente halogenado (e.g., CF_3), o puede tener uno o más carbonos que están sustituidos o reemplazados con un heteroátomo, como NR, O o S (e.g., $-OCH_2CH_2O-$, alquiltioles, tioalcoxi, alquilaminas, etc).

[0022] "Aril" se refiere a un anillo aromático monocíclico o bicílico fusionado que contiene átomo de carbono. "Arileno" siginifica un radical divalente derivado de un grupo arilo. Por ejemplo, un grupo arilo puede ser fenil, indenil, indanil, naftil, o 1,2,3,4-tetrahidronaftalenil, que puede estar opcionalmente sustituido en la posición orto, meta o para.

[0023] "Heteroaril" como se usa aquí, es como se definió para aril anteriormente, donde uno o más de los miembros del anillo es un heteroátomo. Ejemplos de heteroarilos incluyen pero no se limitan a piridil, pirazinil, indolil, indazolil, quinoxalinil, quinolinil, benzofuranil, benzopiranil, benzotiopiranil, benzo[1,3]dioxol, imidazolil, benzo-imidazolil, pirimidinil, furanil, oxazolil, isoxazolil, triazolil, benzotriazolil, tetrazolil, pirazolil, tienil, pirrolil, isoquinolinil, purinil, tiazolil, tetrazinil, benzotiazolil, oxadiazolil, benzoxadiazolil, etc.

[0024] Un "anillo carbocíclico" como se usa aquí, se refiere a un anillo saturado o parcialmente insaturado, monocíclico, bicíclico fusionado o policíclico con puentes que contiene átomos de carbono, que pueden estar opcionalmente sustituidos, por ejemplo, con =O. Ejemplos de anillos carbocíclicos incluyen pero no se limitan a ciclopropil, ciclobutil, ciclopentil, ciclohexil, ciclopropileneo ciclohexanona, etc.

[0025] Un "anillo heterocíclico" como se usa aquí, es como se definió para un anillo carbocíclico anteriormente, donde uno o más carbonos del anillo son un heteroátomo. Por ejemplo, un anillo heterocíclico puede contener N, O, S, -N=, -S-, -S(O), $-S(O)_2-$, o -NR- donde R puede ser hidrogen, C_{1-4}alquil o un grupo protector. Ejemplos de anillos heterocíclicos incluyen pero no se limitan a morfolino, pirrolidinil, pirrolidinil-2-ona, piperazinil, piperidinil, piperidinilona, 1,4-dioxa-8-aza-spiro[4.5]dec-8-il, 1,2,3,4-tetrahidroquinolinil, etc. Anillo heterocíclico, como se usa aquí, puede comprender aminas bicíclicas y diaminas bicíclicas.

[0026] Los términos "la co-administración" o "asociación" o similares, tal como se utiliza en este documento tienen por objeto abarcar la administración de la selección de agentes terapéuticos a un solo paciente, y están destinadas a incluir los regímenes de tratamiento en el que los agentes no son necesariamente administrados por la misma vía de administración o al mismo tiempo.

[0027] El término "combinación farmacéutica", tal como se utiliza en este documento, se refiere a un producto obtenido a partir de la mezcla o combinación de ingredientes activos, e incluye combinaciones tanto fijas y no fijas las de los ingredientes activos. El término "combinación" significa que los ingredientes activos, por ejemplo, un compuesto de fórmula (I) y un co-agente, son administrados a un paciente al mismo tiempo en forma de una entidad única o dosis. El término " combinación no-fija " significa que los ingredientes activos, por ejemplo, un compuesto de fórmula (I) y un co-agente, son administrados a un paciente, ya sea como entidades separadas al mismo tiempo, simultánea o secuencialmente, sin plazos específicos, en el que dicha administración proporciona los niveles de eficacia terapéutica de los ingredientes activos en el cuerpo del paciente. Este último se aplica también a los cócteles de terapia, por ejemplo, la administración de tres o más ingredientes activos.

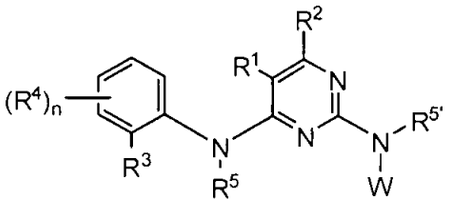
[0028] El término "cantidad terapéuticamente efectiva" se entiende como la cantidad de compuestos objeto que provocan una respuesta biológica o médica de una célula, tejido, órgano, sistema, animal o humano busca obtener el investigador, veterinario, médico u otro clínico.

[0029] El término "administración" o "administrar" el compuesto objeto significa proporcionar un compuesto de la invención y profármacos del mismo a un sujeto en necesidad de tratamiento.

Modos de llevar a cabo la invención

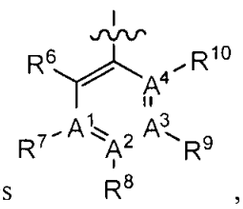
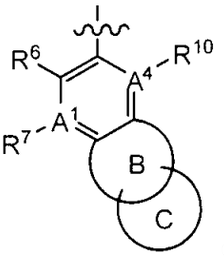
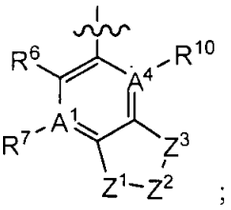
[0030] La invención proporciona nuevos derivados de pirimidina y piridina y composiciones farmacéuticas, y métodos para el uso de dichos compuestos.

[0031] En a unapecto, la invención proporciona la Fórmula (1):



(1)

o sales farmacéuticamente aceptables del mismo; donde

W es  ,  or  ;

A^1 y A^4 son independientemente C o N;

cada A^2 y A^3 es C, o uno de A^2 y A^3 es N donde R^6 y R^7 forman un anillo;

B y C son independientemente un anillo carbocíclico de 5-7 miembros opcionalmente sustituido, aril, heteroaril o un anillo heterocíclico que contiene N, O o S;

Z^1, Z^2 y Z^3 son independientemente NR^{11}, C=O, CR-OR, $(CR_2)_{1-2}$ o =C-R^{12};

R^1 y R^2 son independientemente halo, OR^{12}, $NR(R^{12})$, SR^{12}, o un C_{1-6} alquil, C_{2-6} alquenil o C_{2-6} alquinil, opcionalmente sustituidos; o uno de R^1 y R^2 es H;

R^3 es $(CR_2)_{0-2}SO_2R^{12}$, $(CR_2)_{0-2}SO_2NRR^{12}$, $(CR_2)_{0-2}CO_{1-2}R^{12}$, $(CR_2)_{0-2}CONRR^{12}$ o ciano;

R^4, R^6, R^7 y R^{10} son independientemente un C_{1-6} alquil, C_{2-6} alquenil o C_{2-6} alquinil, opcionalmente sustituidos; OR^{12}, $NR(R^{12})$, halo, nitro, SO_2R^{12}; $(CR_2)_pR^{13}$ o X; o R^4, R^7 y R^{10} son independientemente H;

R, R^5 y $R^{5'}$ son independientemente H o C_{1-6} alquil;

R^8 y R^9 son independientemente C_{1-6} alquil, C_{2-6} alquenil, C_{2-6} alquinil, halo o X, o uno de R^8 y R^9 es H donde R^1 y R^2 forman un anillo; y siempre que uno de R^8 y R^9 es X;

alternativamente, R^1 y R^2, o R^6 y R^7, R^7 y R^8, o R^9 y R^{10}, cuyo están unidos a un átomo de carbono puede formar un anillo carbocíclico monocíclico o fusionado de 5-7 miembros opcionalmente sustituido, aril, o heteroaril o un anillo heterocíclico que comprende N, O y/o S; o R^7, R^8, R^9 y R^{10} están ausentes cuyo están unidos a un N;

R^{11} es H, C_{1-6} alquil, C_{2-6} alquenil, $(CR_2)_pCO_{1-2}R$, $(CR_2)_pOR$, $(CR_2)_pR^{13}$, $(CR_2)_pNRR^{12}$, $(CR_2)_pCONRR^{12}$ o $(CR_2)_pSO_{1-2}R^{12}$;

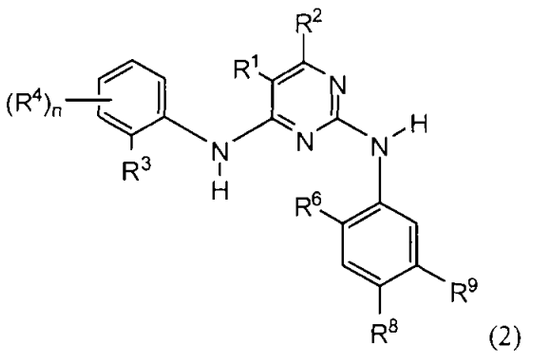
R^{12} y R^{13} son independientemente un anillo carbocíclico de 3-7 miembros saturados o parcialmente insaturado opcionalmente sustituido, o un anillo heterocíclico de 5-7 miembros que comprende N, O y/o S; aril o heteroaril; o R^{12} es H, C_{1-6} alquil;

X es $(CR_2)_qY$, ciano, $CO_{1-2}R^{12}$, $CONR(R^{12})$, $CONR(CR_2)_pNR(R^{12})$, $CONR(CR_2)_pOR^{12}$, $CONR(CR_2)_pSR^{12}$, $CONR(CR_2)_pS(O)_{1-2}R^{12}$ o $(CR_2)_{1-6}NR(CR_2)_pOR^{12}$;

Y es un anillo carbocíclico de 3-12 miembros opcionalmente sustituido, un aril de 5-12 miembros, o un heteroaril de 5-12 miembros o un anillo heterocíclico que comprende N, O y/o S y unidos a un^2 o A^3 o ambos por medio de un átomo de carbono de dicho heteroaril o un anillo heterocíclico donde q en $(CR_2)_qY$ es 0; y

n, p y q son independientemente 0-4.

|0032| En una modalidad, la invención proporciona un compuestos que tienen la Fórmula (2):



(2)

donde R^1 es halo o C_{1-6} alquil;

R^2 es H; o

R^1 y R^2 juntos forman un anillo heteroarilo o heterocíclico de 5-6 miembros opcionalmente sustituido que comprende uno o dos átomos de nitrógeno;

R^6 es isopropoxi o metoxi;

uno de R^8 y R^9 es $(CR_2)_qY$ y el otro es C_{1-6} alquil, ciano, $CO_{1-2}R^{12}$, $CONR(R^{12})$ o $CONR(CR_2)_pNR(R^{12})$;

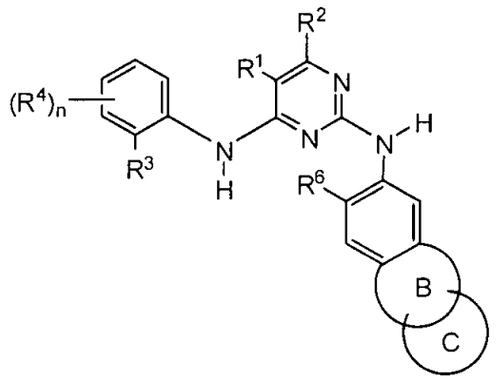
Y es un C_{3-7} cicloalquil, C_{3-7} cicloalquenil, o fenil, opcionalmente sustituidos; o Y es piridil, pirazolil, isoxazolil, imidazolil, tiazolil, benzimidazolil, pirrolidinil, piperazinil, piperidinil, morfolinil, azetidinil, heptametileneimina o octametileneimina, cada uno de los

cuales están unidos a un anillo fenil por medio de un átomo de carbono donde q en $(CR_2)_qY$ es 0;

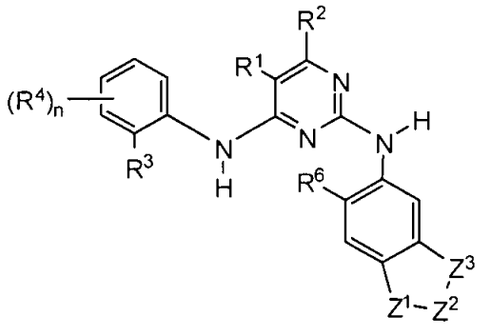
n es 0-1; y

q es 0-4.

[0033] En otra modalidad, la invención proporciona un compuestos que tienen la Fórmula (3A) o (3B):

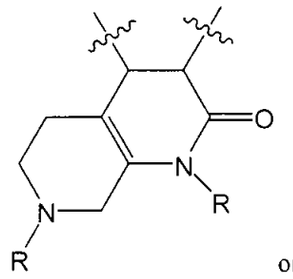


(3A)

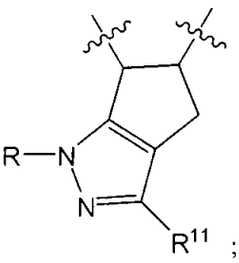


(3B)

donde B y C juntos forman

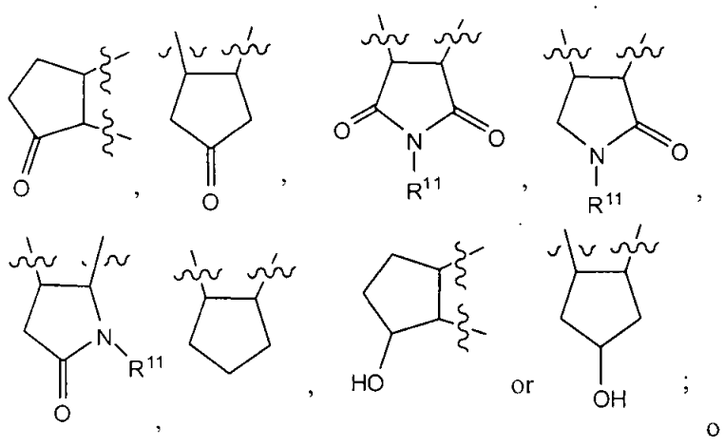


or



;

Z^1, Z^2 y Z^3 juntos forman



o tautómeros de los mismos;

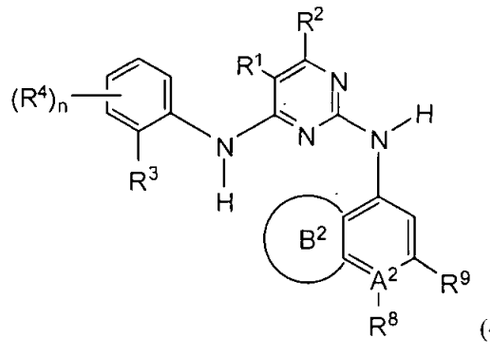
R^1 es halo o C_{1-6} alquil;

R^2 es H; o

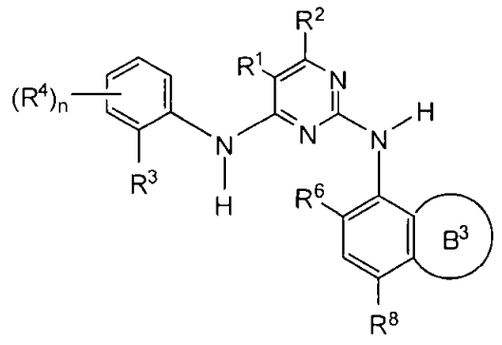
R^1 y R^2 juntos forman un anillo carbocíclico de 5-7 miembros opcionalmente sustituido, aril, o heteroaril o un anillo heterocíclico que comprende N, O y/o S; y

R^6 es isopropoxi o metoxi.

[0034] Aún en otra modalidad, la invención proporciona un compuestos que tienen la Fórmula (4A) o Fórmula (4B):



(4A)



(4B);

donde R^1 es halo o C_{1-6} alquil;

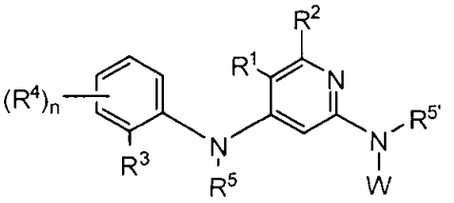
R^2 es H; o

R^1 y R^2 juntos forman un anillo carbocíclico de 5-7 miembros opcionalmente sustituido, aril, o heteroaril o un anillo heterocíclico que comprende N, O y/o S;

R^6 es isopropoxi o metoxi; y

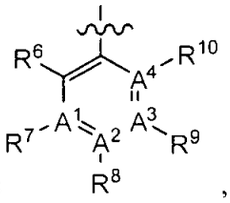
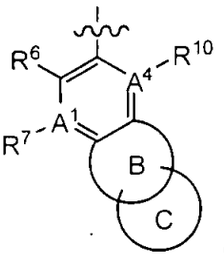
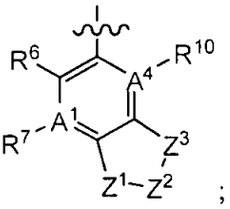
B^2 y B^3 son independientemente un aril o heteroaril de 5-6 miembros opcionalmente sustituido que contiene N, O o S.

[0035] En otro aspecto, la invención proporciona un compuestos que tienen la Fórmula (5):



(5)

o sales farmacéuticamente aceptables del mismo; donde

W es  ,  or  ;

A^1 y A^4 son independientemente C o N;

cada A^2 y A^3 es C, o uno de A^2 y A^3 es N donde R^6 y R^7 forman un anillo;

B y C son independientemente un anillo carbocíclico de 5-7 miembros opcionalmente sustituido, aril, heteroaril o un anillo heterocíclico que contiene N, O o S;

Z^1, Z^2 y Z^3 son independientemente NR^{11}, C=O, CR-OR, $(CR_2)_{1-2}$ o =C-R^{12};

R^1 y R^2 son independientemente halo, OR^{12}, $NR(R^{12})$, SR^{12}, o un C_{1-6} alquil, C_{2-6} alquenil o C_{2-6} alquinil, opcionalmente sustituidos; o uno de R^1 y R^2 es H;

R^3 es $(CR_2)_{0-2}SO_2R^{12}$, $(CR_2)_{0-2}SO_2NRR^{12}$, $(CR_2)_{0-2}CO_{1-2}R^{12}$, $(CR_2)_{0-2}CONRR^{12}$ o ciano;

R^4, R^6, y R^7 y R^{10} cuyos están unidos a un átomo de carbono, son independientemente H, un C_{1-6} alquil, C_{2-6} alquenil o C_{2-6} alquinil, opcionalmente sustituidos; OR^{12}, $NR(R^{12})$, halo, nitro, SO_2R^{12}, $(CR_2)_pR^{13}$ o X; siempre que R^6 y R^7 no son ambos H;

R, R^5 y $R^{5'}$ son independientemente H o C_{1-6} alquil;

R^8 y R^9 son independientemente C_{1-6} alquil, C_{2-6} alquenil, C_{2-6} alquinil, halo o X, o uno de R^8 y R^9 es H; y siempre que uno de R^8 y R^9 es X;

alternativamente, R^1 y R^2, o R^6 y R^7, R^7 y R^8, o R^9 y R^{10}, cuyo están unidos a un átomo de carbono pueden formar a un anillo carbocíclico monocíclico o fusionado de 5-7 miembros

opcionalmente sustituido, aril, o heteroaril o un anillo heterocíclico que comprende N, O y/o S; o R^7, R^8, R^9 y R^{10} están ausentes cuyo están unidos a un N;

R^{11} es H, C_{1-6} alquil, C_{2-6} alquenil, $(CR_2)_pCO_{1-2}R$, $(CR_2)_pOR$, $(CR_2)_pR^{13}$, $(CR_2)_pNRR^{12}$, $(CR_2)_pCONRR^{12}$ o $(CR_2)_pSO_{1-2}R^{12}$;

R^{12} y R^{13} son independientemente un anillo carbocíclico de 3-7 miembros saturado o parcialmente insaturado opcionalmente sustituido, o un anillo heterocíclico de 5-7 miembros que comprende N, O y/o S; aril o heteroaril; o R^{12} es H, C_{1-6} alquil;

X es $(CR_2)_qY$, ciano, $CO_{1-2}R^{12}$, $CONR(R^{12})$, $CONR(CR_2)_pNR(R^{12})$, $CONR(CR_2)_pOR^{12}$, $CONR(CR_2)_pSR^{12}$, $CONR(CR_2)_pS(O)_{1-2}R^{12}$ o $(CR_2)_{1-6}NR(CR_2)_pOR^{12}$;

Y es un anillo carbocíclico de 3-12 miembros opcionalmente sustituido, un anillo de 5-12 miembros, o un heteroaril de 5-12 miembros o un anillo heterocíclico que comprende N, O y/o S y unidos a un^2 o A^3 o ambos por medio de un átomo de carbono de dicho heteroaril o un anillo heterocíclico donde q en $(CR_2)_qY$ es 0; y

n, p y q son independientemente 0-4.

[0036] En cada una de las fórmulas anteriores, Y o R^{13} pueden ser independientemente anillos heterocíclicos, que pueden ser una amina bicíclica o diamina bicíclica. Ejemplos de aminas bicíclicas y diaminas bicíclicas incluyen pero no se limitan a hexanometileneimina opcionalmente sustituida; heptametileneimina; quinuclidina; 3-azabiciclo(3,3,0)octano; 3,8-diazabiciclo[3,2,1]octano; octahidro-1H-pirido[3,4-C]azepina; octahidropirrolizina; 6-azabiciclo[3,2,1]octano; 3-azabiciclo[3,2,1]octano; 2,5-diazabiciclo[2,2,1]heptano; 1-azabiciclo[2,2,1]heptano; 2-azabiciclo[2,2,1]heptano; 1,4-diazabiciclo[4,4,0]decano; 1,4-diazabiciclo[4,3,0]nonano; 1-azabiciclo[3,2,1]octano; 3-azabiciclo[3,3,0]octano; 8-azabiciclo[3,2,1]octano; 3,9-diazabiciclo[4,2,1]nonano; octahidropirrolo[3,4-C]pirrol; octahidropirrolo[3,4-B]pirrol; hexahidropirrolo[3,2-B]pirrol; hexahidropirrolo[3,2-C]pirrol; 1,4-diazacicloóctano; 1,5-diazacicloóctano; 3,7-diazabiciclo[4,2,0]octano; 3,7-diazabiciclo[3,3,1]nonano; octahidropirrolo[3,4-C]piridina; octahidropirrolo[3,4-B]piridina; octahidrociclopenta[C]pirrolidina; hexahidrociclopenta[C]pirrolidina; 8-azabiciclo[3,2,1]octano; decahidroquinolina; decahidroisoquinolina; decahidropirido[3,4-B]azepina; decahidropirido[4,3-B]azepina; 9-azabiciclo[3,3,1]nonano; bispidina; 3-azabiciclo[3,1,0]hexano; 8-azabiciclo[3,2,1]octano; 2-azabiciclo[3.3.1]nonano; tetrahidroquinolina; tetrahidroisoquinolina; 2,5-diazabiciclo[2,2,2]octano; decahidro-2,7-naftiridina; 1,4-diazepano; azonano; octahidro-1H-indol; octahidro-1H-isoindol; 2-azabiciclo[3,3,0]octano; 6-azabiciclo[3,2,1]octano; 7-aza-biciclo[2.2.1]heptano; decahidropirazino[1,2-a]azepina; 3,8-diaza-biciclo[3,2,1]octano; 3-

azabiciclo[3,2,1]octano; 3-aza-triciclo[4,2,1,0(2,5)]nonano; 2,6-diazaspiro[3,5]nonano; 6-azabiciclo[2,1,0]hexano, etc.

[0037] En cada una de las fórmulas anteriores, los átomos de carbono asimétricos pueden estar presentes en configuración (R)-, (S) o (R, S)-. Los compuestos pueden estar presentes en mezclas de isómeros puros o como isómeros, por ejemplo, como enantiómeros puros o diasteroisómeros. La invención también comprende posibles tautómeros de los compuestos inventivos.

[0038] En cada una de las fórmulas anteriores, cada grupo opcionalmente sustituido podrá estar sustituido con C_{1-6} alquil, C_{2-6} alquenil o C_{3-6} alquinil, cada uno de los cuales pueden estar opcionalmente halogenados u opcionalmente, con un carbono, que podrán ser reemplazado o sustituido con N, S, O, o una combinación de los mismos (por ejemplo, hidroxilC_1-C_8alquil, C_1-C_8alcoxiC_1-C_8alquil); halo, aminoácidos, amidino, C_{1-6} alcoxi; hidroxilo, metilenodioxi, carboxi, C_{1-8} alquilcarbónil, C_{1-8} alcoxicarbónil, carbamoil, C_{1-8} alquilcarbamoil, sulfamoil, ciano, oxo, nitro, o un anillo carbocíclico opcionalmente sustituido, anillo heterocíclico, aril o heteroaril como se describió anteriormente.

Farmacología y utilidad

[0039] Los compuestos de la invención y sus sales farmacéuticamente aceptables exponen valiosas propiedades farmacológicas cuyo son evaluados in vitro en ensayos de células libres de quinasa y en ensayos celulares, y por lo tanto son útiles como los productos farmacéuticos.

[0040] En un aspecto, los compuestos de fórmula (1), (2), (3A), (3B), (4A), (4B) o (5) pueden inhibir la actividad de tirosina quinasa de la quinasa del linfoma anaplásico (ALK) y de la proteína de fusión de NPM-ALK. Esta proteína tirosina quinasa resulta de la fusión de un gen de nucleofosmin (NPM) y ALK, haciendo la actividad de la proteína tirosina quinasa de ALK independiente del ligando. La NPM-ALK juega un papel clave en la transmisión de la señal en una serie de células hematopoyéticas y otras células humanas que conllevan a enfermedades hematológicas y neoplásicas, por ejemplo, en el linfoma anaplásico de células grandes (ALCL) y linfomas no Hodgkinianos (NHL), específicamente en ALK + NHL o Alkomas, en los tumores inflamatorios miofibroblásticos (IMT) y neuroblastomas. (Duyster et al. 2001 Oncogene 20, 5623-5637). Además del NPM-ALK, otras fusiones de genes se han identificado en enfermedades neoplásicas y hematológicas en humanos, por ejemplo, TPM3-ALK (una fusión de tropomiosina no muscular con ALK).

[0041] La inhibición de la actividad tirosina quinasa ALK puede demostrarse mediante los métodos conocidos, por ejemplo, mediante el uso del dominio recombinante de ALK en

analogía con el ensayo de VEGF-R-quinasa, descrito en J. Wood et al. Cancer Res. 60, 2178-2189 (2000). En general, los ensayos in vitro utilizando enzimas proteína tirosina-quinasa GST-ALK, se realizan en placas de 96 pozos como un ensayo de unión de filtro en 20 mM Tris HCl, pH = 7.5, 3 mM $MgCl_2$, 10 mM $MnCl_2$, 1 mM DTT, 0.1 μCi/ensayo (=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 enzima ALK. Los ensayos se incuban durante 10 minutos a temperatura ambiente. Las reacciones se terminan añadiendo 50 μl de 125 mM EDTA, y una mezcla de reacción se transfiere a una placa MAIP multipantalla (Millipore, Bedford, MA, EE.UU.), previamente humedecida con metanol, y rehidratados durante 5 min con H_2O. Tras el lavado (0,5% H_3PO_4), las placas son contadas en un contador de centelleo líquido. Valores de CI_{50} se calculan por análisis de regresión lineal del porcentaje de inhibición.

[0042] Compuestos de fórmulas (1), (2), (3A), (3B), (4A), (4B) o (5) pueden inhibir potentemente el crecimiento de celulas murinas BaF3 humanas que sobreexpresan NPM-ALK (DSMZ Deutsche Sammiung von Mikroorganismen und Zelikulturen GmbH, Alemania). La expresión de NPM-ALK podrá lograrse mediante transfección de la línea celular BaF3 con un vector de expresión pCIneo™ (Promega Corp., Madison WI, EE.UU.) que codifica NPM-ALK y la posterior selección de células resistentes G418. Células BaF3 no transfectadas dependen de la IL-3 para la supervivencia celular. En cambio, células BaF3 que expresan NPM-ALK (llamado BaF3-NPM-ALK en adelante) pueden proliferar en ausencia de la IL-3, ya que obtienen la señal de proliferación a través de la NPM-ALK-quinasa. Inhibidores putativos de la quinasa NPM-ALK, así, evita la señal de crecimiento y puede resultar en actividad antiproliferativa. La actividad antiproliferativa de los inhibidores putativos de la NPM-ALK-quinasa puede sin embargo ser superado mediante la adición de IL-3, que proporciona las señales de crecimiento a través de un mecanismo independiente de NPM-ALK. Un sistema celular análogo utilizando la quinasa FLT3, también se ha descrito (véase, Weisberg E et al. Cancer Cell; 1, 433-443 (2002)).

[0043] La actividad inhibitoria de los compuestos de la invención se puede determinar como sigue. En general, células BaF3-NPM-ALK (15.000 / pozo placa de microtitulación) se transfieren a placas de microtitulación de 96 pozos. Los compuestos de prueba son disueltos en dimetil sulfóxido (DMSO) se añaden en una serie de concentraciones (dilución en serie) de tal manera que la concentración final de DMSO no es superior al 1% (v / v). Después de la adición, las placas se incubaron durante dos días, durante los cuales el control de los cultivos sin compuesto de ensayo pueden continuar con dos ciclos de división celular. El crecimiento de las células BaF3-NPM-ALK se mide por medio de tinción YOPRO™ [T Idziorek et al. J. Immunol.

Methods; 185: 249-258 (1995)]: 25 µl de tampón de lisis que comprende 20 mM de citrato de sodio, pH 4.0, 26.8 mM cloruro de sodio, 0,4% NP40, 20 mM EDTA y 20 mM, se añade a cada pozo. La lisis celular se completa en 60 min a temperatura ambiente y la cantidad total de YOPRO™ unido a ADN está determinada por la medición utilizando el lector de pozos Cytofluor II 96-well (PerSeptive Biosystems) con la siguiente configuración: excitación (nm) 485/20 y de emisión (nm) 530/25.

[0044] Valores IC_{50} pueden ser determinados por un sistema asistido por ordenador utilizando la fórmula siguiente:

$$IC_{50} = [(ABS_{test}-ABS_{start})/(ABS_{control}-ABS_{start})] \times 100. \text{ (ABS = absorption)}$$

[0045] El valor de IC_{50} en esos experimentos se da como la concentración de los compuestos de prueba en cuestión que resultan en un conteo celular que es 50% menor que la obtenida mediante el control sin inhibidor. Los compuestos de la invención en forma libre o en forma de sal farmacéuticamente aceptable, pueden presentar propiedades farmacológicas valiosas, por ejemplo, como se indica en las pruebas in vitro descritas en la presente solicitud. En general, los compuestos de la invención tienen valores de IC_{50} desde 1 nM a 10 µM. En algunos ejemplos, los compuestos de la invención tienen valores de IC_{50} de 0,01 µM a 5 µM. En otros ejemplos, los compuestos de la invención tienen valores de IC_{50} de 0,01 µM a 1 µM, o más particularmente a partir del 1 nM a 1 µM. En otros ejemplos, los compuestos de la invención tienen valores de IC_{50} de 1 nm o más de 10 µM. Los compuestos de la invención pueden presentar un porcentaje de inhibición superiores al 50%, o en otras modalidades, pueden presentar un mayor porcentaje de inhibición de aproximadamente el 70%, contra ALK a 10 µM.

[0046] La acción antiproliferativa de los compuestos inventivos podrá determinarse también en las líneas celulares humanas de linfoma de KARPAS-299 (DSMZ Deutsche Sammiung von Mikroorganismen und Zelikulturen GmbH, Braunachweig, Alemania, que se describe en Dirks WG et al. INT. J. Cancer 100, 49-56 (2002)) utilizando la misma métodología descrita anteriormente para la línea celular BaF3-NPM-ALK. En algunas modalidades, los compuestos de la invención pueden presentar actividad inhibitoria con un IC_{50} en el rango de aproximadamente 0,01 a 1 µM. La acción de los compuestos inventivos sobre la actividad de la autofosforilacion de ALK podrá determinarse sobre la línea celular humana de linfoma de KARPAS-299 por medio de un inmunoblot como se describe en Dirks WG et al. Int. J. Cancer 100, 49-56 (2002).

[0047] En otro aspecto, los compuestos de la invención pueden inhibir la quinasa de adhesión (FAK), y pueden ser útiles como productos farmacéuticos para tratar condiciones

provocadas por un mal funcionamiento de las cascadas de señales relacionadas con la FAK, como en el tratamiento de determinados tumores. La inhibición de la señalización de FAK endógena resulta en la reducción de la motilidad y, en algunos casos provoca la muerte celular. Por otro lado, la mejora de la señalización FAK por expresión exógena aumenta la motilidad celular. Además, la la FAK es sobreexpresada en cánceres invasivos y metastásicos epiteliales, mesenquimales, de tiroides y de próstata. En consecuencia, un inhibidor de la FAK es probable que sea un medicamento contra el crecimiento tumoral y la metástasis. Los compuestos de la invención pueden ser útiles para prevenir y/o tratar vertebrados y más concretamente un mamífero, afectado por una enfermedad neoplásica, en particular de tumor de mama, el cáncer de intestino (colon y recto), el cáncer de estómago y el cáncer de ovario y de próstata, cáncer de pulmón de células no pequeñas, cáncer de pulmón de células pequeñas, cáncer de hígado, melanoma, tumor de vejiga y cáncer de cabeza y cuello.

[0048] La relación entre la inhibición de FAK y el sistema inmune se describe por ejemplo, en G.A. van Seventer et al. Eur. J. Immunol. 2001, 31, 1417-1427. Por lo tanto, los compuestos de la invención son, por ejemplo, útiles para prevenir y/o tratar vertebrados y más concretamente un mamífero, afectados por trastornos del sistema inmunitario, las enfermedades o trastornos mediados por los linfocitos T, linfocitos B, los mastocitos y/o eosinófilos, por ejemplo, rechazo agudo o crónico de órganos o tejidoa alo-o xenoinjertos, aterosclerosis, oclusión vascular debido a una lesión vascular, como la angioplastia, la restenosis, la hipertensión, insuficiencia cardíaca, enfermedad pulmonar obstructiva crónica, enfermedades del SNC tales como la enfermedad de Alzheimer o la esclerosis lateral amiotrófica, el cáncer; enfermedades infecciosas como el SIDA; shock séptico o síndrome de distrés respiratorio del adulto, lesion de isquemia/reperfusión, por ejemplo, infarto de miocardio, accidente cerebrovascular, isquemia intestinal, insuficiencia renal o shock hemorrágico o shock traumático.

[0049] En otro aspecto, los compuestos de la invención pueden inhibir la proteína 70 proteína a la cadena zeta (ZAP-70). La interacción de los agentes de la invención con la proteína tirosina quinasa ZAP-70 puede ser demostrada, por ejemplo, por su capácidad para prevenir la fosforilación de LAT-11 (enlace para la activación de células T) por la proteína tirosina-quinasa ZAP-70 humana en solución acuosa. Por lo tanto, los compuestos de la invención pueden ser útiles para la prevención o el tratamiento de trastornos o enfermedades en los que la inhibición de la ZAP-70 desempeña un papel.

[0050] Los compuestos de la invención también pueden inhibir el receptor del factor de crecimiento tipo insulina (IGF-1R), y puede ser útil en el tratamiento de enfermedades mediadas por IGF-1R. Ejemplos de enfermedades mediadas por IGF-1R incluyen pero no se limitan a

enfermedades de proliferación, como tumores, por ejemplo, tumores de mama, renales, de próstata. colorrectal, tiroides, ovario, páncreas, neuronales, pulmón, uterino y gastrointestinales, así como osteosarcomas y melanomas. La eficacia de los compuestos de la invención como inhibidores de la actividad de la tirosina quinasa IGF-1R puede demostrarse mediante una prueba ELISA de captura celular. En este ensayo, se determina la actividad de los compuestos de la invención contra autofosforilation de la IGF-1R inducida por (IGF-1).

[0051] Los compuestos de la invención también pueden ser útiles en el tratamiento y/o prevención de enfermedades o desordenes inflamatorios agudos o crónicos, o enfermedades autoinmunes, por ejemplo artritis reumatoide, osteoartritis, lupus eritematoso sistémico, tiroiditis de Hashimoto, la esclerosis múltiple, miastenia gravis, la diabetes (tipo I y II) y los trastornos asociados a los mismos, las enfermedades respiratorias como el asma o las lesiones inflamatorias del hígado, lesiones glomerulares inflamatorias, manifestaciones cutáneas de desordenes o enfermedades mediadas inmunologícamente, enfermedades de la piel inflamatorias o hiperproliferativas (como la psoriasis, dermatitis atópica, dermatitis de contacto alérgica, dermatitis de contacto irritante y ademas dermatitis eczematosa, dermatitis seborreica), enfermedades oculares inflamatorias, por ejemplo, el síndrome de Sjoegren queratoconjuntivitis o uveítis, enfermedad inflamatoria intestinal, enfermedad de Crohn o colitis ulcerosa.

[0052] De conformidad con lo anterior, la presente invención proporciona:

(1) un compuesto de la invención para su utilización como un farmacéutico;

(2) un compuesto de la invención para su utilización como un inhibidor de ALK, inhibidor de FAK, inhibidores de ZAP-70 y/o inhibidores IGF-1R, por ejemplo para su uso en cualquiera de las indicaciones anteriormente enunciados;

(3) una composición farmacéutica, por ejemplo, para su uso en cualquiera de las indicaciones antes enunciadas, que comprende un compuesto de la invención como ingrediente activo, junto con uno o más diluyentes farmacéuticamente aceptables o vehículos;

(4) un método para el tratamiento de cualquier indicación que figura anteriormente en un sujeto con necesidad del mismo, que comprende administrar una cantidad efectiva de un compuesto de la invención o una composición farmacéutica que comprenda el mismo;

(5) el uso de un compuesto de la invención para la fabricación de un medicamento para el tratamiento o prevención de un enfermedad o condición en que la activación ALK, FAK, ZAP-70 y / o IGF-1R, desempeña un papel o es implicado;

(6) el método como se definió anteriormente en virtud de (4), que comprende la co-administración, por ejemplo, concomitantemente o en secuencia, de una cantidad terapéuticamente eficaz de un compuesto de la invención y una o más sustancias activas, donde

dicho fármaco es útil en alguna de las indicaciones establecidas anteriormente;

(7) un combinación terapéutica que comprende una cantidad efectiva de un compuesto de la invención y uno o más nuevos fármacos, dicho fármaco adicional es útil en alguna de las indicaciones establecidas anteriormente;

(8) uso de un compuesto de la invención para la fabricación de un medicamento para el tratamiento o prevención de una enfermedad que responda a la inhibición de la quinasa anaplásica de linfoma;

(9) de acuerdo con el uso (8), donde la enfermedad a ser tratadas es seleccionado de linfoma anaplásico de células grandes, linfoma no-Hodgkinianos, tumores inflamatorios miofibroblásticos, neuroblastomas y enfermedades neoplásicas;

(10) según el uso (8) o (9), donde el compuesto es farmacéuticamente aceptable; sal de cualquier uno de los ejemplos;

(11) un método para el tratamiento de una enfermedad que responde a la inhibición de la quinasa anaplásica de linfoma, especialmente seleccionados a partir de un enfermedad del linfoma anaplásico de células grandes, limfomas no Hodgkin, tumores inflamatorios miofibroblásticos, neuroblastomas y enfermedades neoplásicas, que comprende la administración de una cantidad eficaz de un compuesto de la invención o una sal farmacéuticamente aceptable del mismo.

Administración y Composiciones farmacéuticas

[0053] En general, los compuestos de la invención se administran en cantidades terapéuticamente eficaces a través de cualquiera de los modos habituales y conocidos aceptables en la materia, ya sea solos o en combinación con uno o más agentes terapéuticos. Una cantidad terapéuticamente eficaz puede variar ampliamente dependiendo de la gravedad de la enfermedad, la edad y la salud relativa del sujeto, la potencia de los compuestos utilizados y otros factores conocidos para aquellos con habilidades normales en la materia. Por ejemplo, para el tratamiento de enfermedades neoplásicas y alteraciones del sistema inmune, la dosis necesaria también varía dependiendo del modo de administración, la condición particular a tratar y el efecto deseado.

[0054] En general, los resultados satisfactorios se indica que se obtuvieron en forma sistémica con dosis diarias de alrededor de 0,01 a alrededor de 100 mg / kg de peso corporal, o especialmente, de aproximadamente 0,03 a 2,5 mg / kg por peso corporal. Una dosis diaria indicada mamíferos grandes, por ejemplo, los seres humanos, pueden estar en el rango de alrededor de 0,5 mg a alrededor de 2000 mg, o más concretamente, de alrededor de 0,5 mg a 100 mg, administrada convenientemente, por ejemplo, divididos en dosis de hasta cuatro veces al día

o en forma retardada. Unidades de formas de dosificación adecuadas para la administración oral comprende aprox. 1 a 50 mg de principio activo.

[0055] Los compuestos de la invención se pueden administrar como composiciones farmacéuticas convencionales por cualquier ruta, por ejemplo, enteral, por ejemplo, por vía oral, por ejemplo, en forma de tabletas o cápsulas; parenteral, por ejemplo, en forma de soluciones o suspensión es inyectablas; o tópica, por ejemplo, en forma de lociones, geles, cremas o ungüentos, o en una forma nasal o supositorio.

[0056] Composiciones farmacéuticas que comprenden un compuesto de la presente invención en forma libre o en forma de sal farmacéuticamente aceptable, en asociación con al menos un portador farmacéuticamente aceptable o diluyente puede fabricarse de forma convencional por procesos de mezcla, granulado, revestimiento, la disolución o liofilización. Por ejemplo, composiciones farmacéuticas que comprenden un compuesto de la invención, en asociación con al menos un vehículo o diluyente farmacéuticamente aceptable, puede fabricarse en forma convencional por la mezcla con un portador farmacéuticamente aceptable o diluyente. Unidades de dosificación para la administración oral contienen, por ejemplo, de alrededor de 0,1 mg a 500 mg de sustancia activa.

[0057] En una modalidad, las composiciones farmacéuticas son soluciones de la sustancia activa, incluyendo las suspensión es o dispersiones, como soluciones acuosas isotónicas. En el caso de composiciones liofilizadas que comprenden el principio solo o junto con un portador como manitol, las dispersiones o suspensión es se pueden fabricar antes de su uso. Las composiciones farmacéuticas pueden ser ésterilizadas y/o contener adyuvantes, tales como conservantes, estabilizantes, humectantes o agentes emulsionantes, promotores de solución, sales para la regulación de la presión osmótica y/o buffers. Conservantes adecuados incluyen, pero no se limitan a los antioxidantes como ácido ascórbico, o los microbicidas, tales como ácido sórbico o ácido benzóico. Las soluciones o suspensión es pueden también comprender agentes para el aumento de la viscosidad, incluyendo pero no limitado a carboximetilcelulosa de sodio, carboximetilcelulosa, dextrano, polivinilpirrolidona, gelatinas o solubilizantes, por ejemplo, Tween 80 (polioxietileno(20)sorbitán mono-oleato).

[0058] Suspensión es oleosas pueden comprender como componente oleoso aceites vegetales, sintéticos o semi-sintéticos, usuales para fines de inyección. Los ejemplos incluyen ésteres de ácidos grasos líquidos que contienen como componente ácido un ácido grado de cadena larga que tenga de 8 a 22 átomos de carbono, o en algunas modalidades, de 12 a 22 átomos de carbono. Ácidos grasos líquidos adecuados incluyen, pero no están limitados a, ácido láurico, ácido tridecílico, ácido mirístico, ácido pentadecílico, ácido palmítico, ácido margarico,

ácido esteárico, ácido Araquídónico, ácido behenico o ácidos insaturados correspondientes, por ejemplo el ácido oleico, ácido elaidico, el ácido erúcico, ácido brassidico y ácido linoleico, y si se desea, puede contener antioxidantes, por ejemplo: vitamina E, 3-caroteno o 3,5-di-terc-butil-hidroxitolueno. El componente de alcohol de estos ácidos grasos puede tener seis átomos de carbono y pueden ser monovalentes o polivalentes, por ejemplo, a unlcohol mono-, di-o trivalente. Componentes adecuados de alcohol incluyen, pero no se limitan a, metanol, etanol, propanol, butanol o pentanol o isómeros de los mismo; glicol y glicerol.

[0059] Otros ácidos grasos adecuados incluyen, pero no se limitan a, oleato etílico, Miristato isopropílico, palmitato de isopropilo, LABRAFIL ® M 2375, (polioxietileno glicerol), LABRAFIL ® M 1944 CS (glicéridos poliglicolizados insaturados, preparado por alcoholisis semillas de aceite de albaricoque y que comprenden glicéridos y éster de polietilenglicol), LABRASOL™ (glicéridos saturados poliglicolizados preparados por alcoholisis de TCM y que comprenden érsteres de glicéridos y de polietilenglicol, todos disponibles en GaKefosse, Francia), y/o MIGLYOL ® 812 (triglicéridos de ácidos grasos saturados de cadena de C_8 a C_{12} de Hüls AG, Alemania), y los aceites vegetales como aceite de algodón, aceite de almendras, aceite de oliva, aceite de ricino, aceite de sésamo, aceite de soja o aceite de cacahuate.

[0060] Composiciones farmacéuticas para la administración oral pueden obtenerse, por ejemplo, mediante la combinación de ingredientes activos con uno o más vehículos sólidos, y si se desea, granulación de la mezcla resultante, y el procesamiento de la mezcla o gránulos por inclusión de nuevos excipientes, para formar tabletas o núcleos de tabletas.

[0061] Vehículos adecuados incluyen, pero no se limitan a, diluentes, tales como azúcares, por ejemplo la lactosa, sacarosa, manitol o sorbitol, preparaciones de celulosa y/o fosfatos de calcio, por ejemplo, el fosfato tricálcico o fosfato ácido de calcio, y también aglutinantes, por ejemplo, como los almidonas, por ejemplo, de maíz, de trigo, de arroz o fécula de patata, metilcelulosa, hidroxipropil metilcelulosa, carboximetilcelulosa de sodio, y/o polivinilpirrolidona y/o, si se desea, desintegrantes, como los almidonas mencionados anteriormente, carboximetil almidón, polivinilpirrolidona cruzada, ácido algínico o una sal del mismo, como el alginato de sodio. Excipientes adicionales incluyen acondicionadores de flujo y lubricantes, por ejemplo, ácido silícico, talco, ácido esteárico o sus sales, como el estearato de magnesio o calcio, y/o polietileno glicol, o sus derivados.

[0062] Núcleos de tabletas pueden ser proporcionados con revestimientos, opcionalmente entéricos, a través de la utilización de, entre otras cosas, soluciones concentradas de azúcar, que pueden comprender las goma arábiga, talco, polivinilpirrolidona, polietilenglicol y/o dióxido de titanio, o una solución de revestimiento adecuada en solventes orgánicos adecuados o mezclas

de solventes, o, para la preparación de recubrimientos entéricos, las soluciones de las preparaciones adecuadas de celulosa, como ftalato de acetilcellulosa o ftalato de hidroxipropilmetilcelulosa. Pueden añadirse tintes y pigmentos a los comprimidos o tabletas revestidas, por ejemplo, para fines de identificación o para indicar las diferentes dosis de ingrediente activo.

[0063] Composiciones farmacéuticas para la administración oral pueden incluir también cápsulas duras que comprenden gelatina o cápsulas blandas selladas que comprenden gelatina y un plastificante, como el glicerol o sorbitol. Las cápsulas duras pueden contener el ingrediente activo en forma de gránulos, por ejemplo, en mezcla con el relleno, como el almidón de maíz, aglutinantes, y/o lubricantes, como talco o estearato de magnesio, y, opcionalmente, estabilizantes. En cápsulas blandas, el ingrediente activo puede estar disuelto o suspendidos en excipientes líquidos adecuados, tales como aceites grasos, aceite de parafina o polietilenglicoles líquidos o ésteres de ácidos grasos de etilen o propilenglicol, a los que se puede agregar estabilizantes y detergentes, por ejemplo ésteres de ácidos grasos de tipo polioxietilen sorbitán.

[0064] Composiciones farmacéuticas adecuadas para la administración rectal, por ejemplo, supositorios que comprenden una combinación de sustancia activa y una base de supositorio. Bases de supositorios adecuadas pueden ser, por ejemplo, triglicéridos naturales o sintéticos, hidrocarburos parafínicos, polietilenglicol o alcanoles superiores.

[0065] Composiciones farmacéuticas adecuadas para la administración parenteral pueden comprender soluciones acuosas de un ingrediente activo en forma soluble en agua, por ejemplo, de una sal soluble en agua, o la inyección de suspensión es acuosas que contienen sustancias aumentadoras de la viscosidad, como por ejemplo la carboximetilcelulosa de sodio, sorbitol y o dextrano, y, si se desea, estabilizantes. El ingrediente activo, opcionalmente junto con excipientes, también puede estar en forma liofilizada y puede prepararse una solución antes de la administración parenteral mediante la adición de solventes adecuados. Soluciones como éstas se utilizan, por ejemplo, para la administración parenteral y pueden ser también empleadas como soluciones para perfusión. La fabricación de inyectablas normalmente se lleva a cabo en condiciones estériles, como es el relleno, por ejemplo, en ampollas o viales, y el sellado de los contenedores.

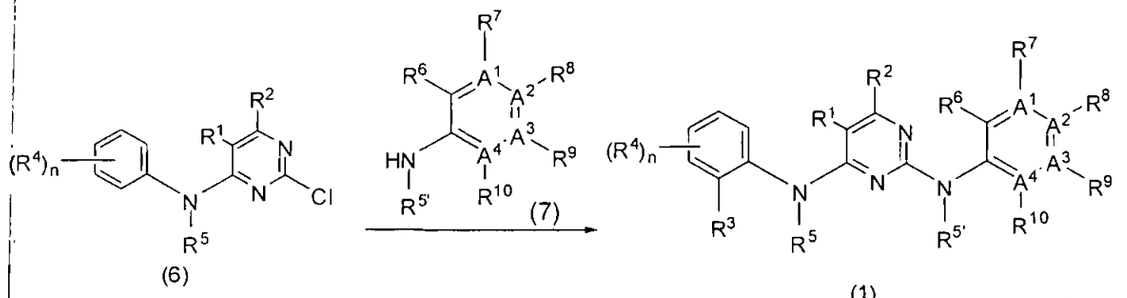
[0066] Los compuestos de la invención se pueden administrar como un único principio activo, o junto con otros fármacos útiles contra las enfermedades neoplásicas o útiles en regímenes de inmunomodulación. Por ejemplo, los compuestos de la invención pueden ser utilizados de acuerdo con la invención en combinación con composiciones farmacéuticas eficaces en diversas enfermedades como se han descrito anteriormente, por ejemplo, con

ciclofosfamida, 5-fluorouracilo, fludarabina, gemcitabina, cisplatino, carboplatino, vincristina, vinblastina, etopósido, irinotecan, paclitaxel, docetaxel, rituxan, doxorubicina, Gefitinib, o imatinib, o también con ciclosporinas, rapamicinas, ascomicinas, o sus análogos inmunosupresores, por ejemplo, ciclosporina A, ciclosporina G, FK-506, sirolimus o everolimus, corticosteroides, por ejemplo, prednisona, ciclofosfamida, azathiopreno, metotrexato, sales de oro, sulfasalazina, antimaláricos, brequinar, leflunomida, mizoribina, ácido micofenolic, micofenolato, mofetil, 15-deoxyspergualina, anticuerpos monoclonales inmuno-supresores, por ejemplo, anticuerpos monoclonales para receptores de leucocitos, por ejemplo, MHC, CD2, CD3, CD4, CD7, CD25, CD28, CD40 l, CD45, CD58, CD80, CD86, CD152, CD137, CD154, ICOS, LFA-1, VLA-4 o sus ligandos, u otros compuestos inmunomoduladores, por ejemplo, CTLA41g.

[0067] La invención también proporciona combinaciones farmacéuticas, por ejemplo, un kit, que comprende a) un primer agente que es un compuesto de la invención divulgada en este documento, en forma libre o en forma de sal farmacéuticamente aceptable, y b) por lo menos un co-agente. El kit puede comprender las instrucciones para su administración.

Procesos para fabricar los compuestos de la invención

[0068] Los compuestos de Fórmula (1) pueden ser preparados siguiendo el esquema de reacción I, en el cual cada sustituyente es como se definió en el Resumen de la invención:



Reaction Scheme I

[0069] Un compuesto de Fórmula (1) puede ser sintetizado por reacción de un compuesto de Fórmula (6) con un compuesto de Fórmula (7) en presencia de un catalizador de paladio (por ejemplo acetato de paladio y similares), un ligando (por ejemplo xantfos y similares) y una base (por ejemplo carbonato de cesio y similares) en un solvente adecuado (por ejemplo, THF, y similares). La reacción se lleva a cabo a un rango de temperatura de aproximadamente 70°C a aproximadamente 180°C y puede tomar 10 min. a 8 horas para completarse.

[0070] Alternativamente, un compuesto de Fórmula (1) puede ser sintetizado por reacción de un compuesto de Fórmula (6) con un compuesto de Fórmula (7) en presencia de un ácido (por ejemplo HCl, TsOH y similares), en un solvente adecuado (por ejemplo, 2-propanol, y similares). La reacción se lleva a cabo a un rango de temperatura de aproximadamente 70°C a aproximadamente 150°C y puede tomar hasta 12 horas para completarse.

Procesos adicionales para fabricar compuestos de la invención

[0071] Los compuestos de la invención, incluyendo sus sales, también se obtienen en la forma de hidratos, o sus cristales pueden incluir por ejemplo el solvente usado para cristalización (presente como solvatos). Las sales pueden ser convertidas a los compuestos en forma libre, por ejemplo, al tratarlas con agentes básicos adecuados, por ejemplo, con carbonatos de metales alcalinos, carbonatos de hidrógeno de metales alcalinos, hidróxidos de metales alcalinos o, como carbonato de potasio o hidróxido de sodio. En vista de la estrecha relación entre los nuevos compuestos en forma libre y aquellas en forma de sus sales, incluyendo las sales que pueden ser utilizados como productos intermedios, por ejemplo, en la purificación o la identificación de los compuestos de la invención, toda referencia a los compuestos libres aquí y en lo sucesivo, se debe entender en el sentido de referirse también a las sales correspondientes, según corresponda.

[0072] Las sales de los compuestos inventivos con un grupo formador de sales puede ser preparado de manera conocida. Sales de adición ácidas de compuestos de Fórmula (1), (2), (3A), (3B), (4A), (4B) o (5) pueden así obtenerse por tratamiento con un ácido o con reactivo de intercambio de iones adecuado. Las sales farmacéuticamente aceptables de los compuestos de la invención pueden formarse, por ejemplo, como sales de adición ácidas, con ácidos orgánicos e inorgánicos, a partir de compuestos de Fórmula (1), (2), (3A), (3B), (4A), (4B) o (5) con un átomo básico de nitrógeno.

[0073] Ácidos inorgánicos adecuados incluyen, pero no se limitan a, ácidos halógenos, como ácido clorhídrico, ácido sulfúrico o ácido fosfórico. Ácidos orgánicos adecuados incluyen, pero no se limitan a ácidos carboxílico, fosfórico, ácido sulfónico o sulfámico, por ejemplo, ácido acético, ácido propiónico, ácido octanóico, ácido decanóico, ácido dodecanóico, ácido glicólico. ácido láctico, ácido fumárico, ácido succínico, ácido adípico, ácido pimélico, ácido subérico, ácido azelaico, ácido málico, ácido tartárico, ácido cítrico, aminoácidos, como el ácido glutámico y ácido aspártico, ácido maleico, ácido hidroximaléico, ácido metilmaléico, ácido ciclohexanocarboxílico, ácido adamantanocarboxílico, ácido benzóico, ácido salicílico, ácido 4 aminosalicílico, ácido ftálico, ácido fenilacético, ácido myélico, ácido cinámico, ácido metano o

etano-sulfónico, ácido 2-hidroxietanosulfónico, ácido etano-1,2-disulfónico, ácido bencenosulfónico, ácido 2-naftalenesulfónico, ácido 1,5-naftaleno-disuifónico, ácido 2 -, 3 o 4 metilbencenonsulfónico, ácido metilsulfúrico, ácido etilsulfúrico, ácido dodecilsulfúrico, ácido ciclohexilsulfámico, ácido N-metil-, N-etil o N-propil sulfámico, u otro ácidos protónico orgánico, como ácido ascórbico.

[0074] Con fines de purificación o aislamiento, también es posible utilizar sales farmacéuticamente inaceptables, por ejemplo picrates o percloratos. Para uso terapéutico, sólo sales farmacéuticamente aceptable o compuestos libres son empleados (en su caso en forma de preparaciones farmacéuticos).

[0075] Los compuestos de la invención en forma no oxidada pueden prepararse a partir de N-óxidos de los compuestos de la invención, por tratamiento con un agente reductor (por ejemplo, azufre, dióxido de azufre, trifenil fosfina, borohidruro de litio, borohidruro de sodio, tricloruro o tribromuro de fósforo, o similares) en un solvente orgánico inerte (por ejemplo, acetonitrilo, etanol, dioxano acuoso, o similares) a 0 a 80 ° C.

[0076] Derivados profármacos de los compuestos de la invención pueden ser preparados por los métodos conocidos por las personas de competencias normales en la materia (por ejemplo, para más detalles, véase Saulnier et al., (1994), Bioorganic y Medicinal Chemistry Letters, Vol. 4, p. 1985). Por ejemplo, prófármacos apropiado pueden ser preparados por reacción de un compuesto de la invención no derivado con un agente carbamilador adecuado (por ejemplo, 1,1-aciloxialquilcarbanoclorhidrato, para-nitrofenil carbonato, o similares).

[0077] Derivados protegidos de los compuestos de la invención pueden ser preparados por medios conocidos por las personas de competencias normales en la materia. Una descripción detallada de las técnicas aplicables en la creación de grupos protectores y su eliminación se puede encontrar en "Protecting Grupos in Organic Chemistry", 3rd edition, John Wiley y Sons, Inc., 1999".

[0078] Los compuestos de la invención pueden ser preparados como sus éstereoisómeros por reacción de una mezcla racémica del compuesto con una solución de un agente de resolución ópticamente activo para formar un par de compuestos diastereoisoméricos, para recuperar los enantiómeros ópticamente puros. La resolución de enantiómeros puede realizarse utilizando derivados diastereoméricos covalentes de los compuestos de la invención, o usando complejos disociables (por ejemplo, sales cristalinas diastereoméricas). Los diasteroisómeros tienen distintas propiedades físicas (por ejemplo, puntos de fusión, puntos de ebullición, solubilidad, reactividad, etc) y puede ser fácilmente separada por el aprovechamiento de estas diferencias. Los diasteroisómeros pueden ser separados por cristalización fraccionada, cromatografía, o por

técnicas de separación/resolución basadas en diferencias de solubilidad. El enantiómero ópticamente puro se recupera, junto con el agente de resolución, por cualquier medio que no de por resultado la racemización. Una descripción más detallada de las técnicas aplicables para la resolución éstereoisómeros de compuestos a partir de una mezcla racémica, pueden encontrarse Jean Jacques, Yre Collet, Samuel H. Wilen, "Enantiomers, Racemates y Resolucións", John Wiley Y Sons, Inc., 1981..

[0079] En resumen, los compuestos de la invención pueden ser fabricados por un proceso, que implica:

(a) Esquema de Reacción I;

(b) opcionalmente convertir un compuesto de la invención en una sal farmacéuticamente aceptable;

(c) opcionalmente, la conversión de una forma de sal de un compuesto de la invención a una forma no-salina;

(d) opcionalmente convertir forma no oxidad de un compuesto de la invención en un N-óxido farmacéuticamente aceptable;

(e) opcionalmente, la conversión de una forma N-óxido de un compuesto de la invención su forma no oxidada;

(f) opcionalmente, la resolución de 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 en un derivado profármaco farmacéuticamente aceptables, y

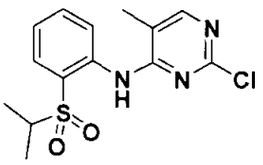
(h) opcionalmente convertir un derivado profármaco de un compuesto de la invención a tu forma no derivada.

[0080] En la medida en que la producción de las materias primas no es particularmente descrita, ya que los compuestos son conocidos o pueden ser preparados por analogía con los métodos conocidos en el arte o como se indica en los ejemplos sucesivos. Una persona de habilidad en el arte apreciará que las transformaciones anteriores son solo representativas de los métodos para la preparación de los compuestos de la presente invención, y que otros métodos bien conocidos también pueden ser utilizados. La presente invención es adicionalmente ejemplificada, pero no se limita, por los siguientes ejemplos que ilustran la preparación de los compuestos de la invención.

Preparación de intermediarios

Intermediario 1

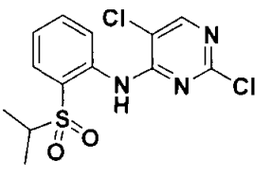
2-cloro-*N*-(2-(*iso*-propilsulfonil)fenil)-5-metilpirimidin-4-amina



[0081] A una suspensión de 730 mg de NaH en una mezcla de DMF/DMSO (25/2.5 ml) se agrega gota a gota a 0°C, 2.53 g (12.69 mmol) de 2-(*iso*-propilsulfonil)benzenamina en DMF/DMSO (10 ml, proporción 9/1). Una solución es agitada 30 minutos a 0°C y 4.11 g (25.3 mmol, 2 eq.) de 2,4-dicloro-5-metilpirimidina diluida en 10 ml de DMF/DMSO (proporción: 9/1) se agrega gota a gota. Una solución es calentada hasta temperatura ambiente y agitada durante la noche. Posteriormente, el producto crudo es directamente cristalizado desde CH_3CN frío en varios lotes para proporcionar 2-cloro-*N*-(2-(*iso*-propilsulfonil)fenil)-5-metilpirimidin-4-amina como cristales pálidos de color cremoso: ESMS *m/z* 326.1 ($M + H^+$).

Intermediario 2

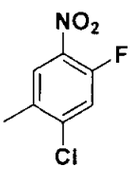
Síntesis de 2,5-dicloro-*N*-(2-(*iso*-propilsulfonil)fenil)pirimidin-4-amina



[0082] Usando el mismo procedimiento descrito para la síntesis de 2-cloro-*N*-(2-(*iso*-propilsulfonil)fenil)-5-metilpirimidin-4-amina, 2,5-dicloro-*N*-(2-(*iso*-propilsulfonil)fenil)pirimidin-4-amina se aisla como un sólido de color cremoso: ESMS *m/z* 346.0 ($M + H^+$).

Intermediario 3

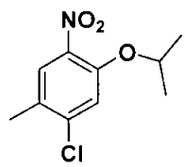
2-cloro-4-fluoro-5-nitrotolueno



[0083] A una solución de 100 g (0.7 mol) de 2-cloro-4-fluorotolueno en 250 ml de H_2SO_4 concentrado se agrega por porciones 85 g (0.875 mol) de KNO_3 a 0°C (adición de la cantidad total de KNO_3 se termina en aproximadamente 1 hora). La mezcla rojiza es calentada lentamente hasta temperatura ambiente durante la noche y extinguida sobre hielo triturado y extraída con EtOAc. Las capas orgánicas se combinan, se secan sobre $MgSO_4$ y se concentran. El aceite crudo es entonces purificado sobre un gran tapón de silica (eluente: 97/3 hexanos/EtOAc) para proporcionar 2-cloro-4-fluoro-5-nitrotolueno a un aceite pálido amarillo que solidifica en resposo. ^{1}H NMR ($CDCl_3$, 400 Mz): 7.97 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 10.4 Hz, 1H), 2.43 (s, 3H).

Intermediario 4

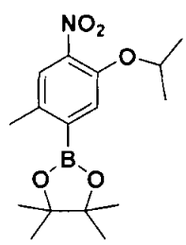
2-cloro-4-*iso*propoxi-5-nitrotolueno



[0084] A una solución de 25 g (0.131 mol) de 2-cloro-4-fluoro-5-nitrotolueno en 250 ml de 2-propanol se agrega 208 g (0.659 mol, 5 eq.) de Cs_2CO_3. La mezcla es agitada a 60°C durante la noche y la mayoría del 2-propanol se evapora a presión reducida. Se agrega agua y una solución es extraída con EtOAc. Las capas orgánicas se combinan, se secan sobre $MgSO_4$, se concentran y el producto crudo filtrado sobre un tapón de sílica (eluente: 95/5 hexanos/EtOAc) para proporcionar 2-cloro-4-*iso*propoxi-5-nitrotolueno como un sólido pálido amarillo esponjoso.

Intermediario 5

éster del ácido 2-metil-4-nitro-5-*iso*propoxi-fenilborónico pinacólico

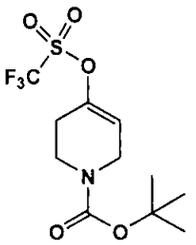


[0085] Una mezcla de 5.09 g 2-cloro-4-*iso*propoxi-5-nitrotolueno (0.02216 mol), 6.20 g (0.02437 mol) de pinacol diborano, 595 mg (0.00212 mol) de PCy_3, 1.014 g (0.00108 mol) de

Pd_2dba_3 y 3.16 g (0.0322 mol) de KOAc en 100 ml de dioxano seco se calienta a 100°C durante la noche. Luego de enfriarse a RT, una solución oscura es filtrada sobre celita y el solvente es evaporado a presión reducida. El aceite crudo es purificado en una columna de cromatografía de sílica gel (eluente: 95/5 hexanos/EtOAc) para proporcionar éster del ácido 2-metil-4-nitro-5-*iso*propoxi-fenilborónico pinacólico como a un aceite que solidifica en resposo. ^{1}H NMR ($CDCl_3$, 400 Mz): 7.51 (s, 1H), 7.44 (s, 1H), 4.70 (m, 1H), 2.48 (s, 3H), 1.36 (d, J = 7.6 Hz, 6H), 1.35 (s, 12H).

Intermediario 6

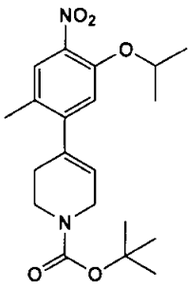
Éster tert-butílico del ácido 4-Trifluorometanosulfoniloxi-3,6-dihidro-2H-piridina-1-carboxílico



[0086] Una solución de *N-tert*-Butoxicarbonil-4-piperidona (10.17 g, 0.05 mol) en THF (100 mL) se agrega gota a gota enfriado (-78 °C), agita vigorosamente la solución de LDA (40 mL de 1.5 M solución en ciclohexanos, 0.06 mol) en THF (100 mL), bajo N_2. La mezcla de reacción se deja a -78 °C por 30 min antes de añadir una solución de fenil trifluorosulfonimida (19.85 g, 0.055 mol) en THF (50 mL). Luego la mezcla de reacción es calentada a temperatura ambiente y agitada por 3 h. La reacción es extinguida a 0 °C con 100 mL de NH_4Cl saturado acuoso y filtrada a través de de Celita. El filtrado se agrega a 100 mL de EtOAc y las capas se separan. La capa orgánica se lava con H_2O, se seca sobre $MgSO_4$ y se concentra. El producto crudo es purificado por cromatografía flash de sílica en columna (0-30% EtOAc en Hexanos como eluente y verificado por TLC con 2% de $KMnO_4$ en EtOH) para proporcionar Éster tert-butílico del ácido 4-Trifluorometanosulfoniloxi-3,6-dihidro-2H-piridina-1-carboxílico como a un aceite amarillo.

Intermediario 7

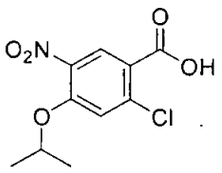
éster tert-butílico del ácido 4-(5-Isopropoxi-2-metil-4-nitro-fenil)-3,6-dihidro-2H-piridina-1-carboxílico



[0087] A una solución del éster del ácido de 2-metil-4-nitro-5-*iso*propoxi-fenilborónico pinacólico (2.04 g, 6.4 mmol) y éster tert-butílico del ácido 4-Trifluorometanosulfoniloxi-3,6-dihidro-2H-piridina-1-carboxílico (3.2 g, 9.6 mmol) en 110 mL de DME/H_2O (10:1 V/V) se agrega $Pd(PPh_3)_4$ (365 mg, 0.32 mmol) y Cs_2CO_3 (4.2 g, 12.8 mmol). La mezcla de reacción se calienta bajo N_2 a 80 °C durante la noche. Luego de enfriarse a temperatura ambiente, la reacción es filtrada a través de Celita y el filtrado es diluido con 100 mL de EtOAc, secuencialmente lavado con H_2O, salmuera, y finalmente se concentra al vacío. El producto crudo es purificado por cromatografía flash de sílica gel (5%-15% EtOAc en Hexanos como eluente) para proporcionar éster tert-butílico del ácido 4-(5-Isopropoxi-2-metil-4-nitro-fenil)-3,6-dihidro-2H-piridina-1-carboxílico como a un aceite amarillo. ^1H NMR (CD_3OD, 400 Mz): 7.59 (s, 1H), 6.96 (s, 1H), 5.67 (broad s, 1H), 4.73 (m, 1H), 4.06 (m, 2H), 3.65 (m, 2H), 2.37 (m, 2H), 2.25 (s, 3H), 1.50 (s, 9H), 1.33 (d, J = 6.0 Hz, 6H).

Intermediario 8

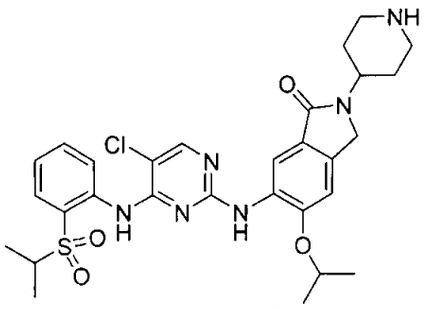
Ácido 2-Cloro-4-isopropoxi-5-nitro-benzóico



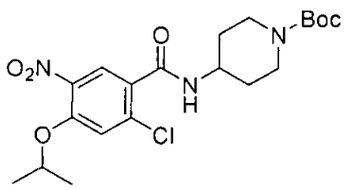
[0088] Una mezcla de ácido 2-cloro-4-fluoro-5-nitro-benzóico (5.0 g, 22.8 mmol) y carbonato de cesio (29.7 g, 91.1 mmol) en 2-propanol (100 mL) se calienta a 50°C durante la noche. El solvente se remueve al vacío y se agrega 100 mL de agua. Se agrega HCl concentrado acuoso gota a gota a esta solución a 0 °C hasta pH=2. El producto precipitado que se forma se aisla por filtración, lavado con agua y secado bajo vacío para dar ácido 2-cloro-4-isopropoxi-5-nitro-benzóico.

Ejemplo 1

6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-piperidin-4-il-2,3-dihidro-isoindol-1-ona (**178**)

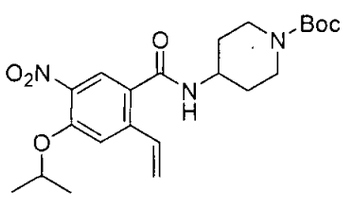


Pasos 1 y 2: éster tert-butílico del ácido 4-(2-Cloro-4-isopropoxi-5-nitro-benzoilamino)-piperidina-1-carboxílico



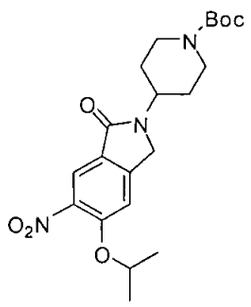
[0089] A una solución de ácido 2-cloro-4-isopropoxi-5-nitro-benzóico (**Intermediario 8,** 10 g, 38.5 mmol) en DCM (200 mL) y DMF (1mL), es lentamente adicionado tionil cloruro (9.17 g, 77 mmol) via jeringa. La mezcla es agitada por 3 horas, y es luego concentrada hasta sequedad. El sólido blanco obtenido, 2-cloro-4-isopropoxi-5-nitro-benzoil cloruro, es secado bajo vacío. A una mezcla de éster tert-butílico del ácido 4-amino-piperidina-1-carboxílico (1.44g, 7.2 mmol) y trietilamina (3 mL, 21.6 mmol) en DCM (100 mL), es lentamente adicionado 2-cloro-4-isopropoxi-5-nitro-benzoil cloruro (2g, 7.2 mmol) disuelto en DCM (10 mL) vía jeringa. La mezcla es agitada a temperatura ambiente por 3 horas, y es luego concentrado. El sólido obtenido es disuelto en etil acetato y se lava con agua y salmuera respectivamente. Luego de evaporación del solvente, el compuesto del título se obtiene como un sólido amarillo claro, y es directamente usado en el próximo paso sin purificación adicional.

Paso 3: éster tert-butílico del ácido 4-(4-Isopropoxi-5-nitro-2-vinil-benzoilamino)-piperidina-1-carboxílico



[0090] A una mezcla de éster tert-butílico del ácido 4-(2-cloro-4-isopropoxi-5-nitro-benzoilamino)-piperidina-1-carboxílico (7.2 mmol) obtenido en el paso anterior, éster dibutílico del ácido vinilborónico (1.72 g, 9.4 mmol) y carbonato de sodio (5.34 g, 50.4 mmol) en THF/H_2O (100/25 mL) se agrega diclorobis(trifenilfosfina) paladio (II) (442 mg, 5% mmol). La mezcla es purgada con N_2 por 3 min y calentada a 90°C bajo N_2 durante la noche en un balón de fondo redondo equipado con un condensador. La mezcla se enfría a temperatura ambiente y se verte en una solución de cloruro de amonio saturada. La mezcla es extraída con etil acetato (3 x 100 mL). Los extractos orgánicos se combinan, lavados con salmuera y se concentran. El producto crudo es purificado en una columna de cromatografía de sílica gel (40% etil acetato en hexanos) para proporcionar éster tert-butílico del ácido 4-(4-isopropoxi-5-nitro-2-vinil-benzoilamino)-piperidina-1-carboxílico como un sólido blanco.

Pasos 4, 5 y 6: éster tert-butílico del ácido 4-(5-Isopropoxi-6-nitro-1-oxo-1,3-dihidro-isoindol-2-il)-piperidina-1-carboxílico



[0091] carboxílico éster tert-butílico del ácido 4-(4-Isopropoxi-5-nitro-2-vinil-benzoilamino)-piperidina-1- obtenido del paso anterior (1.9 g, 4.38mmol) es disuelto en DCM (100 mL) y se enfría a -78 °C. O_3 (g) es burbujeado en una solución hasta que el color de la solución de vuelve azul/gris. Una solución es entonces purgada con N_2 (g) hasta que el color azul desaparece. Una solución es calentada a temperatura ambiente y tratada con resina trifenil fosfina (5 g) pre-tratada en DCM (100 mL). Luego de 30 min, la mezcla es filtrada, el filtrado es concentrado, y el residuo resultante es disuelto en DCM/TFA (100mL / 25 mL). A esta mezcla se agrega trietil silano (4.6 mL, 17.5 mmol). La mezcla resultante es agitada a temperatura ambiente durante la noche. La mezcla de reacción es concentrada y re-disuelta en DCM. La solución de DCM se lava con HCl 1N acuoso (3 x 20 mL). Las capas acuosas combinadas son tratadas con NaOH conc. acuoso hasta pH =12. La capa acuosa es extraída con etil acetato (3 x 30 mL). Las capas orgánicas combinadas se lavan con salmuera, y se secan sobre sulfato de sodio. Un sólido amarillo claro es obtenido luego de evaporación del solvente orgánico.

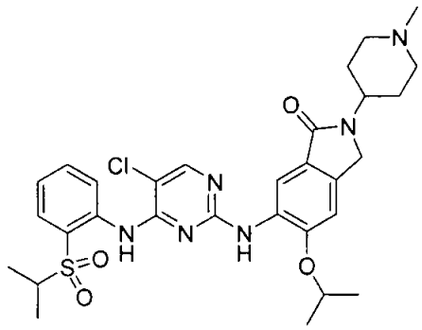
[0092] El sólido es disuelto en una mezcla de metanol y trietilamina (100mL, 9:1 v/v). A ésta mezcla se agrega di-tert-butil dicarbonato (680 mg, 3.1mmol). Luego de agitar a 50 °C por 30 minutos, la mezcla es concentrada y purificada por cromatografía flash en columna de silica gel (eluente: 40~50% etil acetato en hexanos) para proporcionar éster tert-butílico del ácido 4-(5-Isopropoxi-6-nitro-1-oxo-1,3-dihidro-isoindol-2-il)-piperidina-1-carboxílico como un sólido blanco. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.11 (s, 1H), 4.74 (q, 1H), 4.45-4.38 (m, 1H), 4.35 (s, 2H), 2.90-2.80 (m, 2H), 1.85-1.81 (m, 2H), 1.66-1.63 (m, 2H), 1.48 (s, 9H), 1.42 (d, 6H).

Pasos 7, 8 y 9

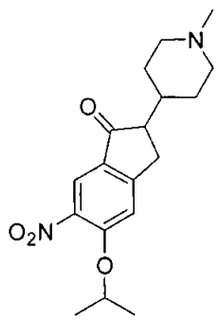
[0093] A una solución de éster tert-butílico del ácido 4-(5-isopropoxi-6-nitro-1-oxo-1,3-dihidro-isoindol-2-il)-piperidina-1-carboxílico del paso previo (850 mg, 2mmol) en metanol, se agrega Pd/C (10% on carbón, 100 mg). La mezcla es hidrogenada bajo 1 atm de gas hidrógeno. Luego de 4 horas, la mezcla es filtrada y se concentra. La anilina obtenida, como un sólido amarillo, es usado para el próximo paso sin purificación adicional. A una mezcla del producto crudo (2 mmol) del paso anterior, (2,5-dicloro-pirimidin-4-il)-[2-(propano-2-sulfonil)-fenil]-amina (**Intermediario 2,** 770mg, 2.2 mmol), carbonato de cesio (1.3g, 4mmol), y xantfos (115 mg, 0.2mmol) en THF (20 mL), se agrega acetato de paladio (22mg, 5% mmol) en un tubo de microondas. La mezcla es purgada con N_2 por 3 min. El tubo sellado se calienta a 150°C por 20 min bajo radiación de microondas. La mezcla se enfría, es filtrada y se concentra. El residuo es purificado por cromatografía flash en columna de silica gel (eluente: 65% etil acetato en hexanos) para proporcionar un sólido amarillo. El sólido es tratado con DCM/TFA (1/1, 10mL) por 1 hora seguido de concentración bajo vacío. La purificación final usando RP LC-MS preparativo que proporciona 6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-piperidin-4-il-2,3-dihidro-isoindol-1-ona (**178**) como un sólido blanco. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 10.13 (s, 1H), 9.60-9.50 (br, 1H), 9.34-9.21 (br, 1H). 8.46 (d, 1H), 8.26 (s, 1H), 8.08 (s, 1H), 7.91 (dd, 1H), 7.71 (m, 1H), 7.34 (t, 1H), 7.03 (s, 1H), 4.30 (m, 1H), 4.53 (m, 1H), 4.33 (s, 2H), 3.62 (m, 2H), 3.21-3.09 (m, 3H), 2.31-2.21 (m, 2H). 2.09-2.05 (m, 2H), 1.41 (d, 6H), 2.30 (d, 6H); ESMS *m/z* 599.2 ($M + H^+$).

Ejemplo 2

6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-(1-metil-piperidin-4-il)-2,3-dihidro-isoindol-1-ona (**181**)



Paso 1: 5-Isopropoxi-2-(1-metil-piperidin-4-il)-6-nitro-indan-1-ona



[0094] A una solución de 5-isopropoxi-6-nitro-2-piperidin-4-il-indan-1-ona (**Ejemplo 1, Paso 5**) en THF (5 mL) y metanol (5 mL) se agrega formaldehído (104.2 uL, 1.39 mmol) y 10 gotas de AcOH secuencialmente. La mezcla de reacción es agitada a temperatura ambiente por 1h, luego cianoborhidruro de sodio (175.1 mg, 2.78 mmol) se agrega en una porción, y la reacción es agitada por adicional 30 min. La reacción es extinguida por acuoso saturadoNH_4Cl y se concentra al vacío para dar un residuo oleoso. Este aceite se particiona entre EtOAc y salmuera, el extracto orgánico se seca sobre Na_2SO_4, es filtrado y se concentra bajo vacío. Cromatografía en silica gel (5% MeOH en DCM) proporciona 5-isopropoxi-2-(1-metil-piperidin-4-il)-6-nitro-indan-1-ona; MS m/z 333.2 (M+1).

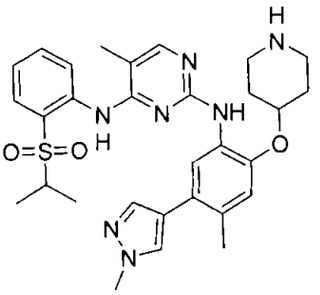
Pasos 2 y 3

[0095] Siguiendo los procedimientos anteriormente descritos **(Ejemplo 1, Pasos 7 y 8)** usando el producto del paso 1 se genera el compuesto del título 6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-(1-metil-piperidin-4-il)-2,3-dihidro-isoindol-1-ona (**181**) como un sólido blanco. ^{1}H NMR 400 MHz (DMSO-d_6 con trazas D_2O) δ 8.46 (d, 1H), 8.35 (s, 1H), 8.09(s, 1H), 7.82(d, 1H), 7.74(t, 1H), 7.36(t,1H), 7.33(s, 1H), 4.75

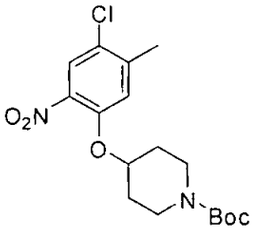
(m, 1H), 4.41(s, 2H), 4,29(m, 1H), 3.65(m, 2H), 3.44(m, 1H), 3.17(t, 2H), 2,79(s, 3H), 2.07(m, 2H), 1.98(d, 2H), 1.28(d, 6H), 1.14(d, 6H); MS m/z 613 (M+1).

Ejemplo 3

5-Metil-N^2-[4-metil-5-(1-metil-1H-pirazol-4-il)-2-(piperidin-4-iloxi)-fenil]-N^4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina (**35**)

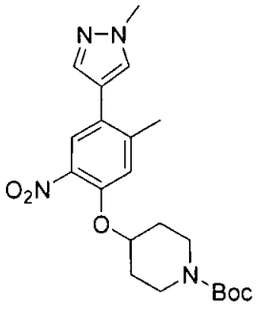


Paso 1: éster tert-butílico del ácido 4-(4-Cloro-5-metil-2-nitro-fenoxi)-piperidina-1-carboxílico



[0096] A una mezcla de 4-Cloro-5-metil-2-nitro-fenol (3.752 g, 20.0 mmol), éster tert-butílico del ácido 4-Hidroxi-piperidina-1-carboxílico (4.83 g, 24 mmol), y trifenilfosfina (6.23 g, 24 mmol) en 75 mL THF se agrega diisopropil asodicarboxilato (4.73 mL, 245 mmol) en varias porciones 22 °C por 1 h. La reacción es agitada a la misma temperatura por 2 hrs adicionales. La mezcla de reacción es concentrada al vacío. El residuo se toma en en 50 mL eter, y se deja reposar a 22 °C por 14 hrs. Los cristales resultantes se remueven por filtración. El filtrado es concentrado al vacío, y el residuo es purificado sobre 330 g SiO_2 en una columna (ISCO) usando un gradiente de 20 a 40% de etil acetato en hexanos como eluente, produciendo el éster tert-butílico del ácido 4-(4-Cloro-5-metil-2-nitro-fenoxi)-piperidina-1-carboxílico como un aceite amarillo oscuro viscoso. MS (ES+); 315.1 (MH+ - C4H8), 393.1 (MNa+).

Paso 2: éster tert-butílico del ácido 4-[5-Metil-4-(1-metil-1H-pirazol-4-il)-2-nitro-fenoxi]-piperidina-1-carboxílico



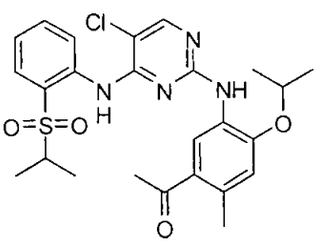
[0097] Una mezcla de éster tert-butílico del ácido 4-(4-Cloro-5-metil-2-nitro-fenoxi)-piperidina-1-carboxílico del paso previo (375.8 mg, 1.01 mmol), 1-Metil-4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-1H-pirazol (Boron Molecular, 224.4 mg 1.08 mmol), fosfato de potasio tribásico monohidrato (392 mg), $Pd_2(dba)_3$ (45 mg), y diciclofosfinobifenil (43 mg) en 4 mL de 1,4-dioxano/H_2O (3/1) se calienta en un tubo sellado a 150 °C por 20 min bajo radiación de microondas. La mezcla de reacción es filtrada a través de un pequeño tapón de Celita, se secan sobre Na_2SO_4 y se concentra. El residuo es purificado usando una columna de SiO_2 (ISCO), produciendo el éster tert-butílico del ácido 4-[5-Metil-4-(1-metil-1H-pirazol-4-il)-2-nitro-fenoxi]-piperidina-1-carboxílico. MS (ES+); 417.3 (MH+), 439.2 (MNa+).

Pasos 3, 4 y 5

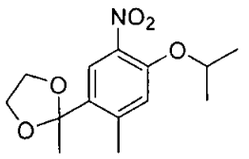
[0098] Utiliza el mismo procedimiento descrito en la síntesis del **Ejemplo 1** (Pasos 7, 8 y 9) y la purificación final usando RP LC-MS preparativa se obtiene 5-Metil-N^2-[4-metil-5-(1-metil-1H-pirazol-4-il)-2-(piperidin-4-iloxi)-fenil]-N^4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina (**35**). MS (ES+): 576.3 (MH+).

Ejemplo 4

1-(5-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-4-isopropoxi-2-metil-fenil)-etanona (**36**)

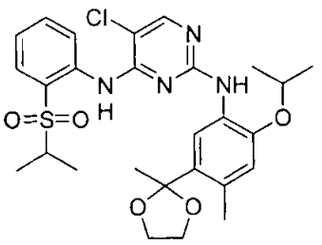


Paso 1: 2-(4-Isopropoxi-2-metil-5-nitro-fenil)-2-metil-[1,3]dioxolano



[0100] Una mezcla de 1-(4-Isopropoxi-2-metil-5-nitro-fenil)-etanona (0.788 g, 3.32 mmol), etileneglicol (1.8 mL), y ácido *p*-toluenosulfónico monohidrato (6.3 mg) en 60 mL de benceno se calienta a reflujo con una trampa Dean-Stark por 18 hrs. La mezcla de reacción es diluida on 100 mL de etil acetato y lavada sucesivamente con 100 mL de $NaHCO_3$ acuoso saturado, H_2O, y salmuera saturada. La fase orgánica se seca sobre Na_2SO_4 anhidro, es filtrada y se concentra al vacío, produciendo 2-(4-Isopropoxi-2-metil-5-nitro-fenil)-2-metil-[1,3]dioxolano como cristales amarillos. MS (ES+): 282.2 (MH+).

Pasos 2 y 3: 5-Cloro-N2-[2-isopropoxi-4-metil-5-(2-metil-[1,3]dioxolan-2-il)-fenil]-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina



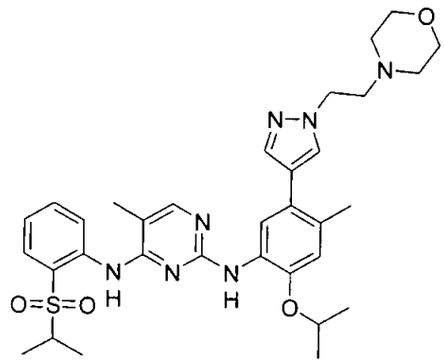
[0101] Utilizando el mismo procedimiento descrito en la síntesis del **Ejemplo 1** (Pasos 7 y 8), usando 2-(4-Isopropoxi-2-metil-5-nitro-fenil)-2-metil-[1,3]dioxolano del paso previo como material inicial y se purificó usando cromatografía de silica gel (gradiente 2% to 20% EtOAc en hexanos) se obtiene el 5-Cloro-N2-[2-isopropoxi-4-metil-5-(2-metil-[1,3]dioxolan-2-il)-fenil]-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina como un sólido blanco. MS (ES+): 561.2 (MH+).

Paso 4

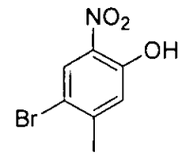
[0102] Una solución de 5-Cloro-N2-[2-isopropoxi-4-metil-5-(2-metil-[1,3]dioxolan-2-il)-fenil]-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina del paso previo (84 mg, 0.15 mmol) en 5 mL 1,4-dioxano es tratada con 1 mL de HCl acuoso 1N a 22 °C por 2 hrs. La reacción se desarrolla y proporciona 1-(5-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-4-isopropoxi-2-metil-fenil)-etanona (**36**). MS (ES+): 517.2 (MH+).

Ejemplo 5

N^2-{2-Isopropoxi-4-metil-5-[1-(2-morfolin-4-il-etil)-1H-pirazol-4-il]-fenil}-5-metil-N^4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina (**37**)

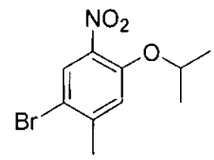


Paso 1: 4-Bromo-5-metil-2-nitro-fenol



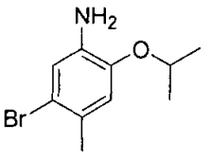
[0103] 4-Bromo-3-metil-fenol (1.122 g, 6.00 mmol) y $Yb(CF_3SO_3)_3$ (372 mg) en 30 mL diclorometano es tratada con 0.38 mL de HNO_3 conc. a 22 °C. Luego de agitar a la misma temperatura por 1 hr, una adición de 0.1 mL de HNO_3 conc.se agrega, y la reacción es agitada por una hora adicional. La mezcla de reacción se lava con H_2O, se seca sobre sulfato de magnesio anhidro, se filtra y se concentra. El residuo es purificado usando una columna de SiO_2 (ISCO), produciendo una mezcla de 4-Bromo-5-metil-2-nitro-fenol como cristales amarilloa y su sub-producto regioisómero como cristales anaranjados.

Paso 2: 1-Bromo-4-isopropoxi-2-metil-5-nitro-benceno



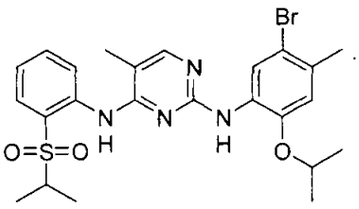
[0104] A una mezcla de 4-Bromo-5-metil-2-nitro-fenol del paso previo (0.66 g, 2.84 mmol), 2-propanol (0.262 mL), y trifenilfosfina (894 mg) en 10 mL de THF se agrega diisopropil asodicarboxilato (0.671 mL) at 22 °C. La mezcla de reacción es concentrada al vacío. El residuo es purificado usando una columna de SiO_2 (ISCO), produciendo 1-Bromo-4-isopropoxi-2-metil-5-nitro-benceno como un sólido amarillo claro.

Paso 3: 5-Bromo-2-isopropoxi-4-metil-fenilamina



[0105] A 1-Bromo-4-isopropoxi-2-metil-5-nitro-benceno del paso previo (0.734 g, 2.68 mmol) y hierro (polvo, 325 mesh, 1.05 g) en 20 mL de etanol se agrega 1 mL de HCl acuoso 1N con enfriamiento en un baño de hielo. Luego de esta adición, la reacción se calienta a reflujo por 2 hrs. luego una adición de 0.5 g de hierro se agrega y la reacción se calienta a reflujo por 2 hrs adicionales. La mezcla de reacción se enfría y se filtra a través de un cojin de Celita. El filtrado es concentrado al vacío, produciendo 5-Bromo-2-isopropoxi-4-metil-fenilamina como a un aceite anaranjado. El producto es usado en el próximo paso sin purificación adicional.

Paso 4: N2-(5-Bromo-2-isopropoxi-4-metil-fenil)-5-metil-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina



[0106] 5-Bromo-2-isopropoxi-4-metil-fenilamina del paso previo (537 mg, 2.20 mmol) y 2-cloro-*N*-(2-(*iso*-propilsulfonil)fenil)-5-metilpirimidin-4-amina (**Intermediario 1**, 652 mg, 2.00 mmol) en presencia de ácido metanosulfónico (0.143 mL) en 4 mL 2-propanol se condensan a 140 °C por 30 min en un tubo sellado bajo radiación de microondas. Posteriormente, N2-(5-Bromo-2-isopropoxi-4-metil-fenil)-5-metil-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina es obtenido. MS (ES+): 535.1 (MH+).

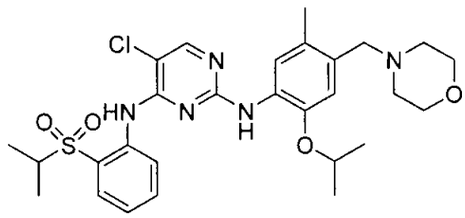
Paso 5

[0107] Una mezcla de N2-(5-Bromo-2-isopropoxi-4-metil-fenil)-5-metil-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina del paso previo (53 mg, 0.099 mmol), 4-{2-[4-(4,4,5,5-Tetrametil-[1,3,2]dioxaborolan-2-il)-pirazol-1-il]-etil}-morfolina (Boron Molecular, 61 mg 0.20 mmol), K_3PO_4 (58 mg), $Pd_2(dba)_3$ (10 mg), y triciclohexilfosfina (8 mg) en 1 mL de 1,4-dioxano/H2O (3/1 v/v) se calienta en un tubo sellado a 150 °C por 20 min bajo radiación de microondas. La mezcla de reacción es filtrada a través de un pequeño tapón de Celita y se

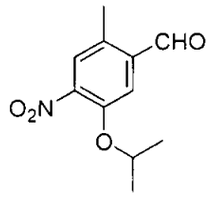
concentra. La purificación final usando RP LC-MS preparativa proporciona N2-{2-Isopropoxi-4-metil-5-[1-(2-morfolin-4-il-etil)-1H-pirazol-4-il]-fenil}-5-metil-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina (**37**). MS (ES+): 634.3 (MH+).

Ejemplo 6

5-Cloro-N2-(2-isopropoxi-5-metil-4-morfolin-4-ilmetil-fenil)-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina (**60**)



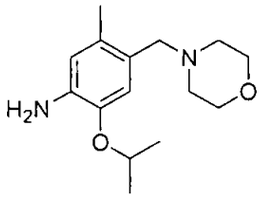
Pasos 1 y 2: 1-Cloro-5-isopropoxi-2-metil-4-nitro-benceno



[0108] A una mezcla de 1-cloro-2-metil-4-nitro-5-isopropoxi-benceno (**Intermediario 4**, 870 mg, 3.77mmol), ácido vinilborónico dibutil éster (1.24 mL, 5.6 mmol), y carbonato de sodio (2.8 g, 26.4mmol) en THF/H_2O (20/5 mL) se agrega diclorobis(trifenilfosfina) paladio (II) (132 mg, 5% mmol). El tubo de reacción es sellado, la mezcla es purgada con N_2 por 3 min y luego calentada a 90°C bajo N_2 durante la noche. La reacción se enfría a temperatura ambiente y se vierte en una solución de cloruro de amonio saturada. La mezcla de reacción cruda es extraída con etil acetato (3 x 100 mL). Los extractos orgánicos se combinan, son lavados con salmuera y se concentran. El producto crudo es purificado en una columna de cromatografía de sílica gel (10% etil acetato en hexanos) para proporcionar 1-metil-5-nitro-4-propoxi-2-vinil-benceno como un sólido amarillo. 1-Metil-5-nitro-4-propoxi-2-vinil-benceno obtenido del paso anterior (360 mg, 1.63mmol) es disuelto en DCM (20 mL) y se enfría a -78 °C. O_3 (g) es burbujeado en una solución hasta que el color de la solución sea azul/gris. La solución es entonces purgada con N_2 (g) hasta que el color azul desaparece. La solución es calentada a temperatura ambiente y tratada con resina de trifenilfosfina (2 g) pre-tratada en DCM (30 mL). Luego de 30 min, la mezcla es filtrada, y el filtrado es concentrado para proporcionar 2-metil-4-nitro-5-propoxi-benzaldehído como un sólido amarillo.

250

Pasos 3 y 4: 2-Isopropoxi-5-metil-4-morfolin-4-ilmetil-fenilamina



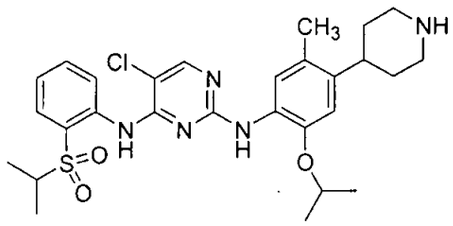
[0109] A una solución de 2-metil-4-nitro-5-propoxi-benzaldehído obtenido en el paso anterior (34 mg, 0.152 mmol) en MeOH/THF (0.5/0.5 mL), se agrega ácido acético (5 gotas). La mezcla es agitada a temperatura ambiente por 1 hora. Cianoborhidruro de sodio (20 mg, 0.30 mmol) es luego adicionado. Luego de agitar por 30 min, la reacción es extinguida por adición de una solución de cloruro de amonio acuoso saturado. La mezcla de reacción es extraída con etil acetato (3 x 5 mL). Las fases orgánicas se combinan y se concentran para proporcionar el producto amina como a un aceite amarillo que es directamente usado en el próximo paso sin purificación adicional. A una solución del producto obtenido en el paso anterior en metanol (5 mL), se agrega Pd/C (10% on carbón, 2 mg). La mezcla es hidrogenada bajo 1 atm de hidrógeno. Luego de 4 horas, la mezcla es filtrada y se concentra. El producto anilina obtenido (amarillo sólido), es usado en el próximo paso sin purificación adicional.

Paso 5

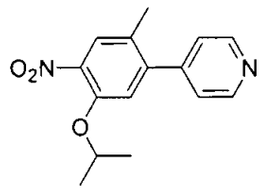
[0110] A una mezcla del producto anilina obtenido en el paso anterior (0.152 mmol), (2,5-dicloro-pirimidin-4-il)-[2-(propano-2-sulfonil)-fenil]-amina (**Intermediario 2**, 52 mg, 0.152 mmol), carbonato de cesio (99 mg, 0.30 mmol) y xantfos (8 mg, 0.02mmol) en THF (2 mL), se agrega acetato de paladio (2 mg, 5% mmol) en un tubo de microondas. La mezcla es purgada con N_2 por 3 min y luego el tubo sellado se calienta a 150 °C por 20 min. bajo radiación de microondas. La reacción es filtrada, concentrada, y purificada por mass-trigger RP LC-MS preparativa para proporcionar el compuesto del título 5-Cloro-N^2-(2-isopropoxi-5-metil-4-morfolin-4-ilmetil-fenil)-N^4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina (**60**) como un sólido amarillo: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35(s, 1H), 8.38 (d, 1H0, 7.93 (d, 1H), 7.59 (m, 2H), 7.41-7.36 (m, 2H), 4.70-4.63(br, 1H), 4.30-4.18 (br, 2H), 4.15-4.10 (br, 2H), 4.00-3.97 (br, 2H), 3.52-3.46 (br, 2H), 3.20 (m, 1H), 2.95-2.84 (br, 2H), 2.24 (s, 3H), 1.31 (d, 12H); ESMS *m/z* 574.2 ($M + H^+$).

Ejemplo 7

5-Cloro-N^2-(2-isopropoxi-5-metil-4-piperidin-4-il-fenil)-N^4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina (**66**)

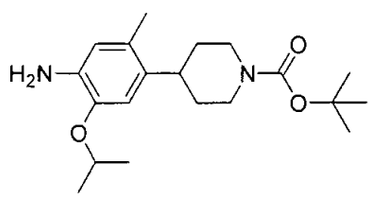


Paso 1: 4-(5-Isopropoxi-2-metil-4-nitro-fenil)-piridina



[0111] ácido 4-Piridinaborónico (147 mg, 1.20 mmol, 1.1 equiv.) es disuelto en una mezcla de 2:1 v/v dioxano y H_2O (15 mL) y N_2 es burbujeado por 5 minutos. Tris(dibenzilideno acetona)dipaladio (0) (100 mg, 0.109 mmol, 0.1 equiv.), 2-diciclohexilfosfina-2'-6'-dimetoxi bifenil (112 mg, 0.272 mmol, 0.25 equiv.), 1-cloro-5-isopropoxi-2-metil-4-nitro-benceno (**Intermediario 4**, 250 mg, 1.09 mmol, 1.0 equiv.) y K_3PO_4 (462 mg, 2.18 mmol, 2.0 equiv.) son adicionados bajo una manta de N_2. El recipiente de reacción es sellado y calentado con radiación de microondas a 150 °C por 20 min. Luego de enfriarse a temperatura ambiente, la reacción es diluida con etil acetato y lavada con NaOH acuoso 1N (2x), la capa orgánica luego se seca sobre Na_2SO_4 y filtrada. Luego de concentración, el producto crudo es purificado por cromatografía de silica gel (gradiente de hexanos a 30% etil acetato en hexanos) para dar 4-(5-Isopropoxi-2-metil-4-nitro-fenil)-piridina como un sólido marron: ESMS *m/z* 273.1 ($M + H^+$).

Pasos 2 y 3: éster tert-butílico del ácido 4-(4-Amino-5-isopropoxi-2-metil-fenil)-piperidina-1-carboxílico



[0112] 4-(5-Isopropoxi-2-metil-4-nitro-fenil)-piridina del paso anterior (438 mg, 1.61 mmol) disuelto en ácido acético (30 mL) es tratada con TFA (0.24 mL, 3.22 mmol) y PtO_2 (176 mg,

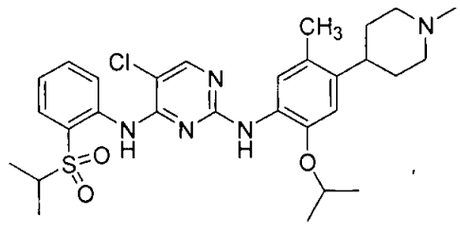
40% w/w). La mezcla de reacción es agitada vigorosamente bajo 1 atm. de H_2 por 36 horas. La mezcla de reacción es filtrada y el filtrado es concentrado bajo vacío. El residuo resultante es diluido con etil acetato y lavado con NaOH acuoso 1N (2x), la capa orgánica luego se seca sobre Na_2SO_4 y es filtrada. Luego de concentración, el producto crudo (391 mg) es disuelto en CH_2Cl_2 anhidro (30 mL). Se agrega TEA (0.44 mL, 3.15, 2 equiv.) seguido de Boc_2O (344 mg, 1.57 equiv, 1 equiv.). La reacción es agitada a temperatura ambiente por 30 min. La reacción es concentrada bajo vacío. El residuo resultante es purificado por cromatografía de silica gel (gradiente de hexanos a 30% etil acetato en hexanos) para dar éster tert-butílico del ácido 4-(4-amino-5-isopropoxi-2-metil-fenil)-piperidina-1-carboxílico como una espuma pegajosa: ESMS *m/z* 293.1 $(M\text{-}t\text{Bu}+H)^+$.

Pasos 4 y 5

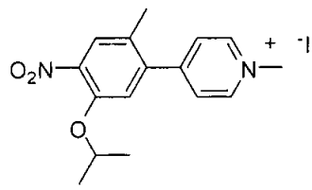
[0113] éster tert-butílico del ácido 4-(4-Amino-5-isopropoxi-2-metil-fenil)-piperidina-1-carboxílico (170 mg, 0.488 mmol) del paso anterior, (2,5-Dicloro-pirimidin-4-il)-[2-(propano-2-sulfonil)-fenil]-amina (**Intermediario 2**, 169 mg, 0.488 mmol, 1 equiv.), xantfos (28 mg, 0.049 mmol, 0.1 equiv.), acetato de paladio (5.5 mg, 0.024 mmol, 0.05 equiv.), y Cs_2CO_3 (477 mg, 1.46 mmol, 3 equiv.) son disueltos en THF anhidro (6 mL). N_2 es burbujeado a la mezcla de reacción por 5 minutos y luego el recipiente de reacción es sellado y calentado con radiación de microondas a 150 °C por 20 min. La reacción es filtrada y el filtrado concentrado bajo vacío. Luego de concentración, el producto crudo es purificado por cromatografía de silica gel (gradiente de hexanos a 30% etil acetato en hexanos) para dar el éster tert-butílico del ácido 4-(4-{5-cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-metil-fenil)-piperidina-1-carboxílico como una película amarilla: ESMS *m/z* 658.3 $(M + H^+)$. Este producto (105 mg, 0.160 mmol) es disuelto en CH_2Cl_2 (3 mL) y tratado con TFA (3 mL). Luego de 45 min., la reacción es concentrada bajo vacío. HCl 1N en Et_2O (5 mL x 2) se agrega causando la precipitación del producto HCl sal. El solvente se remueve por decantación. La 5-Cloro-N^2-(2-isopropoxi-5-metil-4-piperidin-4-il-fenil)-N^4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina resultante (**66**) es secado a bajo fuerte vacío, generó un polvo blanco apagado: ^{1}H NMR (400 MHz, DMSO-d_6 + trace D_2O) δ 8.32 (s, 1H), 8.27 (d, 1H), 7.88 (d, 1H), 7.67 (dd, 1H), 7.45 (dd, 1H), 7.42 (s, 1H), 6.79 (s, 1H), 4.56-4.48 (m, 1H), 3.49-3.32 (m, 3H), 3.10-2.91 (m, 3H), 2.09 (s, 3H), 1.89-1.77 (m, 4H), 1.22 (d, 6H), 1.13 (d, 6H); ESMS *m/z* 558.1 $(M + H^+)$.

Ejemplo 8

5-Cloro-N^2-[2-isopropoxi-5-metil-4-(1-metil-piperidin-4-il)-fenil]-N^4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina (**67**)

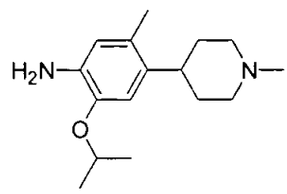


Paso 1: 4-(5-Isopropoxi-2-metil-4-nitro-fenil)-1-metil-piridino yoduro



[0114] 4-(5-Isopropoxi-2-metil-4-nitro-fenil)-piridina (**Ejemplo 7, Paso 1,** 217 mg, 0.797 mmol) es disuelto en THF anhidro (9 mL). Yodometano (0.10 mL, 1.61 mmol, 2 equiv.) se agrega y la reacción es agitada a 40 °C en un tubo sellado por 2 días. Los volátiles se remueven bajo vacío generó 4-(5-Isopropoxi-2-metil-4-nitro-fenil)-1-metil-piridino yoduro como un sólido marron: ESMS *m/z* 287.1 (M^+).

Pasos 2 y 3: 2-Isopropoxi-5-metil-4-(1-metil-piperidin-4-il)-fenilamina



[0115] 4-(5-Isopropoxi-2-metil-4-nitro-fenil)-1-metil-piridino yoduro del paso previo (0.697 mmol) es disuelto en CH_3OH (20 mL) y enfriado a 0 °C. $NaBH_4$ (264 mg, 6.97 mmol, 10 equiv.) es lentamente adicionado. Luego que esta adición se completa, el baño de enfriamiento se remueve y la reacción es agitada a temperatura ambiente por 1 h. La reacción es extinguida por la lenta adición de HCl acuoso 1N (14 mL). El CH_3OH es parcialmente removido por vacío. El residuo resultante se particiona entre EtOAc y NaOH acuoso 1N. Se agrega NaOH acuoso 50% hasta que la capa acuosa tenga un pH >12. La capa de EtOAc se lava con NaOH acuoso 1N (2x), la capa orgánica luego se seca sobre Na_2SO_4, es filtrada, y se concentra bajo vacío. Luego de concentración, el producto crudo (175 mg) es disuelto en ácido acético (10 mL). TFA

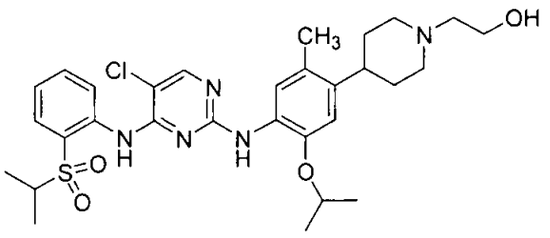
(0.15 mL, 3 equiv.) y PtO_2 (53 mg, 30% w/w) son adicionados y la reacción es puesta bajo 50 psi H_2 gas en un Parr Shaker por 14 h. La mezcla de reacción es filtrada y el filtrado es concentrado bajo vacío. El residuo resultante se particiona entre EtOAc y NaOH acuoso 1N. Se agrega NaOH acuoso 50% adicional hasta que la capa acuosa tenga un pH >12. La capa de EtOAc se lava con NaOH acuoso 1N (2x), la capa orgánica luego se seca sobre Na_2SO_4, es filtrada, y se concentra bajo vacío para dar 2-Isopropoxi-5-metil-4-(1-metil-piperidin-4-il)-fenilamina que es usado en el Paso 4 sin purificación adicional: ESMS *m/z* 263.2 ($M + H^+$).

Paso 4

[0116] Utilizando el mismo procedimiento descrito en la síntesis del **Ejemplo 7** (Paso 4) y la purificación final usando RP LC-MS preparativa, se proporciona 5-Cloro-N^2-[2-isopropoxi-5-metil-4-(1-metil-piperidin-4-il)-fenil]-N^4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina (**67**) como un polvo pálido amarillo: (HCl sal, DMSO-d_6 + trace D_2O) δ 8.28 (s, 1H), 8.19 (d, 1H), 7.86 (d, 1H), 7.66 (dd, 1H), 7.45 (dd, 1H), 7.37 (s, 1H), 6.77 (s, 1H), 4.56-4.49 (m, 1H), 3.51-3.37 (m, 3H), 3.16-3.08 (m, 2H), 2.98-2.88 (m, 1H), 2.77 (s, 3H), 2.05 (s, 3H), 1.90-1.81 (m, 4H), 1.19 (d, 6H), 1.11 (d, 6H); ESMS *m/z* 572.2 ($M + H^+$).

Ejemplo 9

2-[4-(4-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-metil-fenil)-piperidin-1-il]-etanol (**72**)

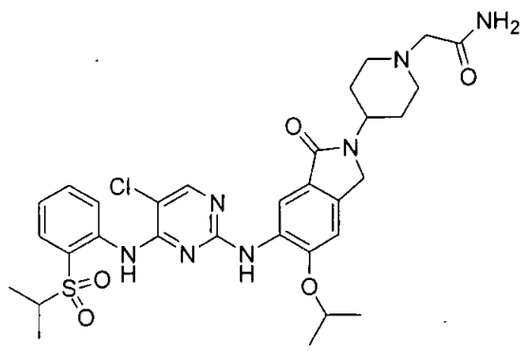


[0117] 5-Cloro-N^2-(2-isopropoxi-5-metil-4-piperidin-4-il-fenil)-N^4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina (**Ejemplo 7**, 0.087 mmol) es disuelto en DMF anhidro (1 mL). TEA (0.04 mL, 0.262 mmol, 3 equiv.) se agrega seguido de 2-bromo-etanol (0.019 mL, 0.262 mmol, 3 equiv.) disuelto en DMF anhidro (0.7 mL). El recipiente de reacción es sellado y calentado a 70 °C por 12 h. Luego de enfriarse a temperatura ambiente, la reacción es diluida con etil acetato y lavada con NaOH acuoso 1N (5x), la capa orgánica luego se seca sobre Na_2SO_4 y ex filtrada. Luego de concentración, el producto crudo es purificado usando RP LC-MS preparativa para dar 2-[4-(4-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-

ilamino}-5-isopropoxi-2-metil-fenil)-piperidin-1-il]-etanol (**72**) como a unmarillo polvo: ESMS *m/z* 602.2 ($M + H^+$).

Ejemplo 10

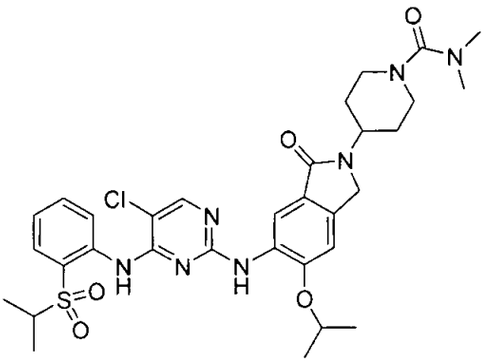
2-[4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro-isoindol-2-il)-piperidin-1-il]-acetamida (**149**)



|0118| A una mezcla de 6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-piperidin-4-il-2,3-dihidro-isoindol-1-ona (**Ejemplo 1**, 20 mg, 0.033 mmol) y trietilamina (23 uL, 0.165 mmol) en DMF (1.5 mL), se agrega 2-bromo-acetamida (10 mg, 0.066 mmol). La mezcla es agitada a 60 °C por 4 horas. La reacción es filtrada y el filtrado es purificado por mass-trigger RP LC-MS preparativa para proporcionar el compuesto del título 2-[4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro-isoindol-2-il)-piperidin-1-il]-acetamida (**136**) como un sólido blanco: ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.41 (d, 1H), 8.27 (s, 1H), 8.21 (br, 1H), 7.93 (dd, 1H), 7.73 (m, 1H), 7.40 (dd, 1H), 7.30 (s, 1H), 4.52 (s, 2H), 4.45-4.37 (m, 1H), 4.19-4.15 (br, 2H), 3.87-3.78 (br, 2H), 2.37-2.19 (m, 2H), 2.20-2.15 (m, 1H), 1.40 (d, 6H), 1.25 (d, 6H); ESMS *m/z* 656.2 ($M + H^+$).

Ejemplo 11

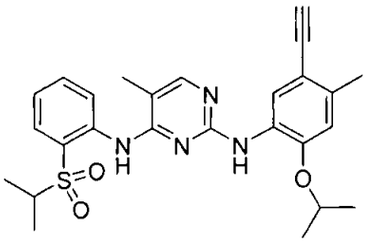
dimetilamida del ácido 4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro-isoindol-2-il)-piperidina-1-carboxílico (**155**)



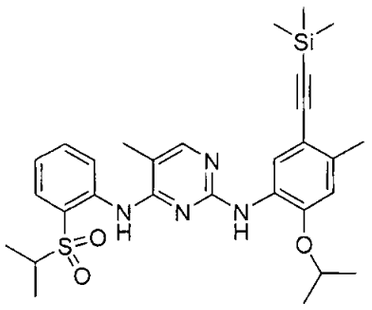
[0119] A una mezcla de 6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-piperidin-4-il-2,3-dihidro-isoindol-1-ona (**Ejemplo 1**, 20 mg, 0.033 mmol) y trietilamina (23 uL, 0.165 mmol) en DMF (1.5 mL) se agrega cloruro de dimetilcarbamil (11 mg, 0.1 mmol). La mezcla es agitada a temperatura ambiente por 1 hora. La reacción es filtrada y el filtrado es purificado por mass-trigger RP LC-MS preparativa para proporcionar el compuesto del título dimetilamida del ácido 4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro-isoindol-2-il)-piperidina-1-carboxílico (**155**) como un sólido blanco: ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.29 (s, 1H), 8.26 (br, 1H), 7.96 (dd, 1H), 7.93 (s, 1H), 7.72(dd, 1H), 7.48 (dd, 1H), 7.35 (s, 1H), 4.50 (s, 2H), 4.35-4.29 (m, 1H), 3.83 (d, 2H), 3.38-3.30 (m, 2H), 3.02-2.95 (m, 3H), 2.88 (s, 6H), 1.88-1.84 (m, 3H), 1.36 (d, 6H), 1.25 (d, 6H); ESMS *m/z* 670.2 ($M + H^+$).

Ejemplo 12

N2-(5-Etinil-2-isopropoxi-4-metil-fenil)-5-metil-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina (**257**)



Paso 1: N2-(2-Isopropoxi-4-metil-5-trimetilsilaniletinil-fenil)-5-metil-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina



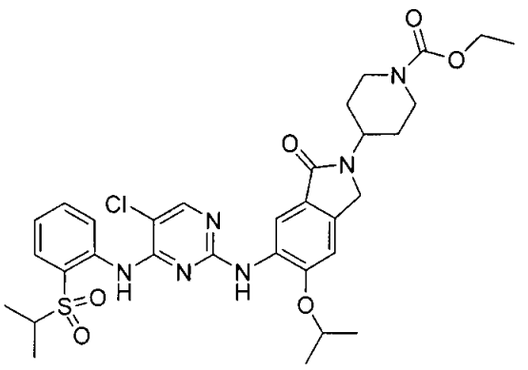
[0120] Una mezcla de N2-(5-Bromo-2-isopropoxi-4-metil-fenil)-5-metil-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina (**Ejemplo 5, Paso 4**, 110 mg, 0.21 mmol), etinil-trimetil-silano (0.14 mL), N,N-diisopropil etilamina (0.10 mL), $PdCl_2(PhCN)_2$ (12 mg), $^tBu_3PHBF_4$ (17 mg), y CuI (4 mg) en 1 mL 1,4-dioxano es agitada a 22 °C por 20 hrs seguido de calentamiento a 60 °C por 2 hrs adicionales. La mezcla de reacción es filtrada a través de un pequeño tapón de Celita y se concentra. El residuo es purificado sobre una columna de 4 g SiO_2 (ISCO) usando un gradiente de 0 a 20% de etil acetato en hexanos como eluente, produciendo N2-(2-Isopropoxi-4-metil-5-trimetilsilaniletinil-fenil)-5-metil-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina como a unmarillo viscoso aceite.

Paso 2

[0121] Una solución de N2-(2-Isopropoxi-4-metil-5-trimetilsilaniletinil-fenil)-5-metil-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina del paso previo (0.102 g, 0.18 mmol) en 2.5 mL THF es tratada con TBAF (0.5 mL, 1M en THF) y 30 µL AcOH a 22 °C por 2 hrs. La mezcla de reacción es concentrada y el residuo es purificado usando un columna de 4g de SiO_2 (ISCO), produciendo N2-(5-Etinil-2-isopropoxi-4-metil-fenil)-5-metil-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina (**257**). MS (ES+): 479.2 (MH+).

Ejemplo 13

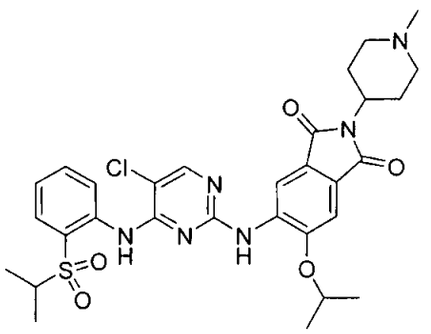
éster etílico del ácido 4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro-isoindol-2-il)-piperidina-1-carboxílico (**175**)



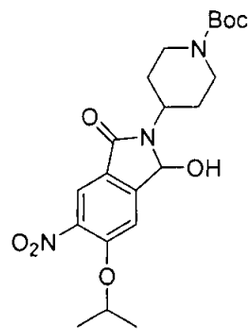
[0122] A una mezcla de 6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-piperidin-4-il-2,3-dihidro-isoindol-1-ona (**Ejemplo 1,** 15 mg, 0.025 mmol) y trietilamina (37.5 uL, 0.25 mmol) en DMF (0.5 mL), se agrega etil cloroformato (5.4 mg, 0.05 mmol). La mezcla es agitada a temperatura ambiente por 1 hora. La mezcla de reacción cruda es purificada por mass-trigger RP LC-MS preparativa para proporcionar el compuesto del título éster etílico del ácido 4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro-isoindol-2-il)-piperidina-1-carboxílico (**175**) como un sólido blanco. ^{1}H NMR 400 MHz (DMSO-d_6 con trazas D_2O) δ 8.55 (d, 1H), 8.32 (s, 1H), 8.14 (s. 1H), 7.82 (dd,1H), 7.74 (t, 1H), 7.34 (t, 1H), 7.28 (s, 1H), 4.73 (m, 2H), 4.39 (s, 2H), 4.12 (m, 2H), 4.06 (q, 2H), 3.46 (m, 1H), 2.92 (m 2H), 1.76 (m, 2H), 1.68 (m, 2H), 1.29 (d, 6H), 1.20 (t, 3H), 1.17 (d, 6H); MS m/z 671 (M+1).

Ejemplo 14

5-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-6-isopropoxi-2-(1-metil-piperidin-4-il)-isoindol-1,3-diona (**176**)

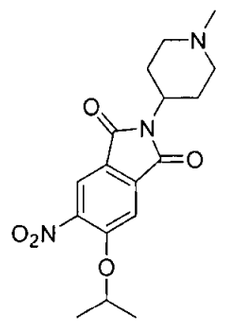


Paso 1: éster tert-butílico del ácido 4-(1-Hidroxi-6-isopropoxi-5-nitro-3-oxo-1,3-dihidro-isoindol-2-il)-piperidina-1-carboxílico



[0123] éster tert-butílico del ácido 4-(4-Isopropoxi-5-nitro-2-vinil-benzoilamino)-piperidina-1-carboxílico (**Ejemplo 1, Paso 3,** 1.2 g, 2.77 mmol) disuelto en 50 mL de DCM se enfría a -78 °C. Gas ozono es burbujeado a esta solución hasta que el material inicial es consumido y luego gas de nitrogen es burbujeado a la solución por 5 min. La mezcla de reacción es calentada a temperatura ambiente. Resina de trifenilfosfina (2.77 g) en 10 mL de DCM se agrega y la mezcla resultante es agitada por 1.5 h. La resina se remueve por filtración y el filtrado es concentrado. Cromatografía de silica gel (5% MeOH en DCM) proporciona el éster tert-butílico del ácido 4-(1-Hidroxi-6-isopropoxi-5-nitro-3-oxo-1,3-dihidro-isoindol-2-il)-piperidina-1-carboxílico; MS m/z 336.2 ($M-Boc + H^+$).

Pasos 2, 3 y 4: 5-Isopropoxi-2-(1-metil-piperidin-4-il)-6-nitro-indan-1,3-diona



[0124] A una solución de éster tert-butílico del ácido 4-(1-Hidroxi-6-isopropoxi-5-nitro-3-oxo-1,3-dihidro-isoindol-2-il)-piperidina-1-carboxílico del paso previo (173.9 mg, 0.4 mmol) en DMF (4 mL) se agrega dicromato de piridina (286.5 mg, 0.8 mmol) en una porción. Luego de agitar a temperatura ambiente por 2 h, La mezcla de reacción se verte en 25 mL de agua y el producto es extraído con EtOAc. Los extractos orgánicos se secan sobre Na_2SO_4, son filtrados y se concentra al vacío para dar éster tert-butílico del ácido 4-(5-isopropoxi-6-nitro-1,3-dioxo-1,3-

dihidro-isoindol-2-il)-piperidina-1-carboxílico crudo, que es directamente usado en el próximo paso sin purificación adicional.

[0125] A una solución de éster tert-butílico del ácido 4-(5-isopropoxi-6-nitro-1,3-dioxo-1,3-dihidro-isoindol-2-il)-piperidina-1-carboxílico generado en el paso anterior en 3 mL de DCM se agrega TFA (3 mL). La mezcla de reacción es agitada a temperatura ambiente por 1 h. Luego de concentración, se agrega agua (5 mL) a la mezcla de reacción cruda, la mezcla resultante es neutralizada para dar un pH=8 por adición de $NaHCO_3$, y el producto es extraído con DCM. Los extractos orgánicos se secan sobre Na_2SO_4, son filtrados y se concentran al vacío para dar 5-isopropoxi-6-nitro-2-piperidin-4-il-isoindol-1,3-diona crudo, que es directamente usado en el próximo paso sin purificación adicional.

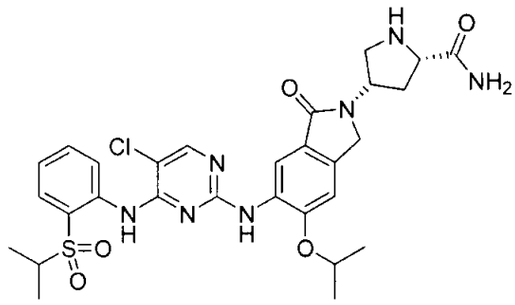
[0126] A una solución de the 5-isopropoxi-6-nitro-2-piperidin-4-il-isoindol-1,3-diona generado en el paso anterior en THF (5 mL) y metanol (5 mL) son adicionados formaldehído (30 uL, 0.4 mmol) y 2 gotas de AcOH secuencialmente. La mezcla de reacción es agitada a temperatura ambiente por 1h, luego se agrega cianoborhidruro de sodio (50.4 mg, 0.8 mmol) en una porción y la mezcla resultante es agitada por un tiempo adicional de 30 min. La reacción es extinguida por adición de NH_4Cl acuoso saturado seguido de concentración al vacío para dar un residuo oleoso. Este aceite se particiona entre EtOAc y salmuera. El extracto orgánico se seca sobre Na_2SO_4, es filtrado y se concentra. Cromatografía de silica gel (5% MeOH en DCM) proporciona 5-isopropoxi-2-(1-metil-piperidin-4-il)-6-nitro-indan-1,3-diona; MS m/z 347.2 (M+1).

Pasos 5 y 6

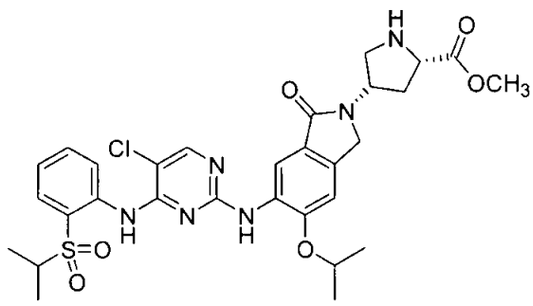
[0127] Siguiendo los procedimientos anteriormente descritos **(Ejemplo 1, Pasos 7 y 8)** usando el producto del paso 4 se genera el compuesto del título 5-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-6-isopropoxi-2-(1-metil-piperidin-4-il)-isoindol-1,3-diona (**176**) como un sólido amarillo. ^1H NMR 400 MHz (DMSO-d_6 con trazas D_2O) δ 8.44 (s, 2H), 8.39 (s, 1H), 7.87 (dd, 1H), 7.78 (dt, 1H), 7.45 (s, 1H), 7.41 (m, 1H), 4.91(m, 2H), 4.25(m, 2H), 3.51 (m, 3H), 3.10(m, 2H), 2.77(s, 3H), 1.80(m, 2H), 1.35(d, 6H), 1.13(d, 6H); MS m/z 627 (M+1).

Ejemplo 15

amida del ácido (2S, 4S)-4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro-isoindol-2-il)-pirrolidina-2-carboxílico (177)



Paso 1: éster metílico del ácido (2S, 4S)-4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro-isoindol-2-il)-pirrolidina-2-carboxílico



[0128] Siguiendo los procedimientos anteriormente descritos **(Ejemplo 1)** usando *N*-Boc-*cis*-4-amino-L-prolina metil éster en lugar de de éster tert-butílico del ácido 4-amino-piperidina-1-carboxílico, se generate el éster metílico del ácido (2S, 4S)-4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro-isoindol-2-il)-pirrolidina-2-carboxílico; MS m/z 643.2 (M+1).

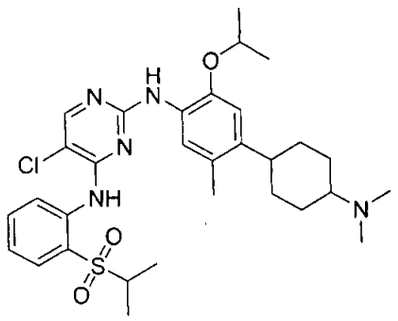
Paso 2

[0129] éster metílico del ácido (2S, 4S)-4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro-isoindol-2-il)-pirrolidina-2-carboxílico generado en el Paso 1 (20 mg, 0.03 mmol) es disuelto en solución de amoniaco 7N en MeOH (3 mL, 21 mmol). La solución resultante se calienta usando radiación de microondas a 120 °C por 1 h. Luego de enfriarse a temperatura ambiente, La mezcla de reacción es concentrada al vacío, neutralizada a pH=8 con $NaHCO_3$ saturado acuoso, y extraída con DCM. Los extractos orgánicos se secan sobre Na_2SO_4, se filtran, y se concentran al vacío para dar amida del ácido (2S, 4S)-4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-

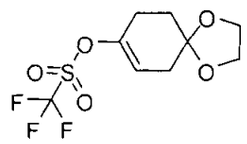
ilamino}-5-isopropoxi-1-oxo-1,3-dihidro-isoindol-2-il)-pirrolidina-2-carboxílico (**177**) como un sólido amarillo. ^{1}H NMR 400 MHz (DMSO-d_6 con trazas D_2O) δ 8.47(d, 1H), 8.25 (s, 1H), 8.07 (s, 1H), 7.78 (dd, 1H), 7.68 (m, 1H), 7.31(t, 1H), 7,24 (s, 1H), 4,71 (m, 2H), 4.43 (dd, 2H), 3.60 (m, 1H), 3.44 (m, 1H), 3.35 (m,1H), 2.63 (m, 1H), 2.28 (m, 1H), 1.22 (d, 6H), 1.10 (d, 6H); MS m/z 628 (M+1).

Ejemplo 16

5-Cloro-N2-[4-(4-dimetilamino-ciclohexil)-2-isopropoxi-5-metil-fenil]-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina (**21**)

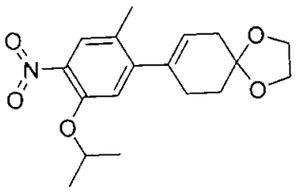


Paso 1: 1,4-dioxaspiro[4.5]dec-7-en-8-il trifluorometanosulfonato



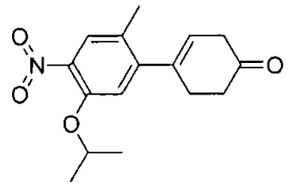
[0130] Una solución de KHMDS 0.5M en tolueno (4.7 mL, 2.34 mmol) se agrega A una solución de 1,4-dioxaspiro[4.5]decan-8-ona (1.80 mmol) y N-feniltrifluorometanosulfonimida (2.34 mmol) en THF seco (18 mL) a -78°C bajo argón. Luego de agitar a -78°C por 4 horas, la mezcla es extinguida con H_2O, extraída con dietil eter y secada con $MgSO_4$. Luego del desarrollo y cromatografía flash en sílica (hexano/EtOAc 90:10), se aisla el 1,4-dioxaspiro[4.5]dec-7-en-8-il trifluorometanosulfonato: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.66 (m, 1H), 3.98 (m. 4H), 2.53 (m, 2H), 2.40 (m, 2H), 1.90 (t, 2H). MS (ES+): 289.0 $(M+1)^+$.

Paso 2: 8-(5-isopropoxi-2-metil-4-nitrofenil)-1,4-dioxaspiro[4.5]dec-7-eno



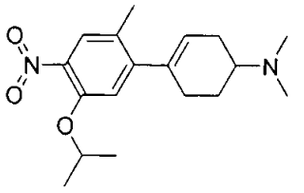
[0131] A una solución agitada del 1,4-dioxaspiro[4.5]dec-7-en-8-il trifluorometanosulfonato (0.03 mmol) y 2-(5-isopropoxi-2-metil-4-nitrofenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (**Intermediario 5**, 0.04 mmol) en THF (3 mL), que contiene $[Pd(PPh_3)_4]$ (0.013 mmol) y $K_3PO_4 \cdot H_2O$ (0.045 mmol), se calienta a 80°C bajo argón por 16 horas. Luego de desarrollarla y cromatografía flash en silica (hexano/EtOAc 4:1), el 8-(5-isopropoxi-2-metil-4-nitrofenil)-1,4-dioxaspiro[4.5]dec-7-eno es obtenido. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (s, 1H), 6.82 (s, 1H), 5.74 (m, 1H), 4.65 (m, 1H), 4.04 (m. 4H), 2.47 (m, 4H), 2.27 (s, 3H), 1.89 (t, 2H), 1.29 (d. 6H). MS (ES+): 334.16 $(M+1)^+$.

Paso 3: 4-(5-isopropoxi-2-metil-4-nitrofenil)ciclohex-3-enona



[0132] Una solución de 8-(5-isopropoxi-2-metil-4-nitrofenil)-1,4-dioxaspiro[4.5]dec-7-eno (0.1 mmol) en 2.5 mL de TFA y CH_2Cl_2 (1:4 v/v), es agitada a temperatura ambiente por 6 horas. Luego de desarrollarla y cromatografía flash en silica (hexano/EtOAc 4:1), el 4-(5-isopropoxi-2-metil-4-nitrofenil)ciclohex-3-enona es obtenido. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (s, 1H), 6.81 (s, 1H), 5.73 (m, 1H), 4.62 (m, 1H), 3.07 (m, 2H), 2.68 (m, 4H), 2.27 (s, 3H), 1.37 (d. 6H). MS (ES+): 290.13 $(M+1)^+$.

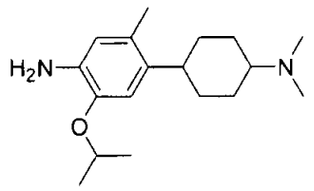
Paso 4: 4-(5-isopropoxi-2-metil-4-nitrofenil)-N,N-dimetilciclohex-3-enamina



[0133] A una solución de 4-(5-isopropoxi-2-metil-4-nitrofenil)ciclohex-3-enona (0.1 mmol) y dimetilamina (0.11 mmol) en 2 mL de 1,2-dicholoroetano, se agrega AcOH (0.1 mmol) y

$NaBH(OAc)_3$ (0.11 mmol). La mezcla de reacción es agitada a temperatura ambiente por 10 horas. Luego de desarrollarla y cromatografía flash en silica (CH_2Cl_2/MeOH 9:1), el 4-(5-isopropoxi-2-metil-4-nitrofenil)-N,N-dimetilciclohex-3-enamina es obtenido. MS (ES+): 319.19 $(M+1)^+$.

Paso 5: 4-(4-(dimetilamino)ciclohexil)-2-isopropoxi-5-metilanilina



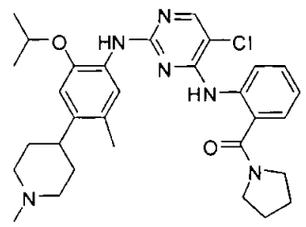
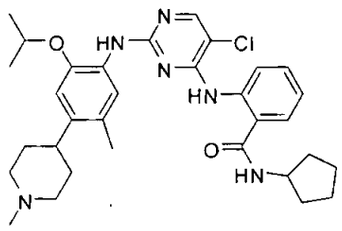
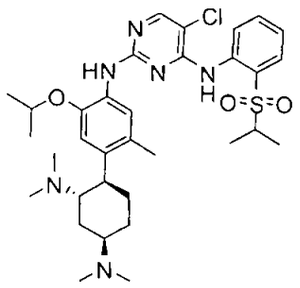
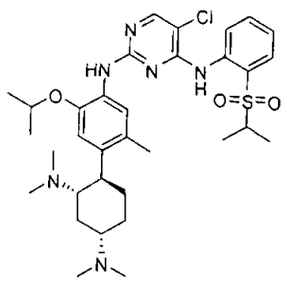
[0134] A una solución de 4-(5-isopropoxi-2-metil-4-nitrofenil)-N,N-dimetilciclohex-3-enamina (0.1 mmol) en 10 mL de MeOH, se agrega Pd/C (5 mg) bajo argón. La suspensión es agitada bajo 1 atm. H_2 por 6 horas. Luego de filtrarla, el solvente se remueve y el 4-(4-(dimetilamino)ciclohexil)-2-isopropoxi-5-metilanilina es obtenido. MS (ES+): 291.24 $(M+1)^+$.

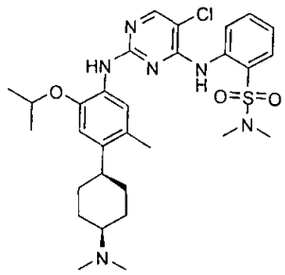
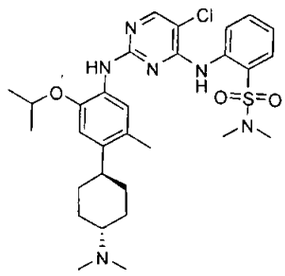
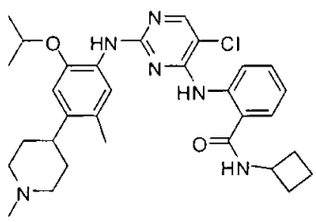
Paso 6

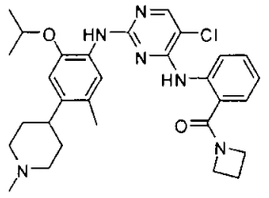
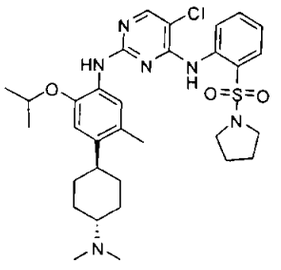
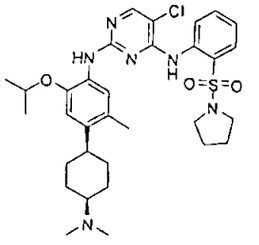
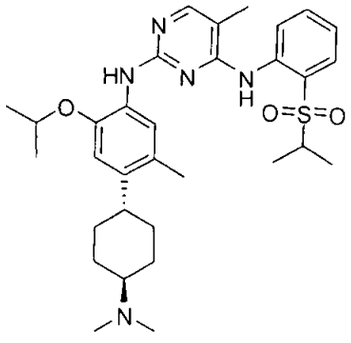
[0135] Siguiendo el procedimeinto previamente descrito **(Ejemplo 7, Paso 4)** usando el producto del paso 5 se genera el compuesto del título 5-Cloro-N2-[4-(4-dimetilamino-ciclohexil)-2-isopropoxi-5-metil-fenil]-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina (**21**). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.36-8.38 (d, 1H), 8.20 (s, 1H), 7.97-7.99 (m, 1H), 7.69-7.73 (m, 1H), 7.46--7.52 (m, 2H), 6.89-7.02 (d, 1H), 4.60-4.66 (m, 1H), 3.37-3.39 (m, 1H), 3.00 (s, 3H), 2.90 (s, 3H), 2.17-2.22 (m, 4H), 1.64-2.01 (m, 8H), 1.25-1.32 (m, 12H); MS (ES+): 600.3 $(M+1)^+$.

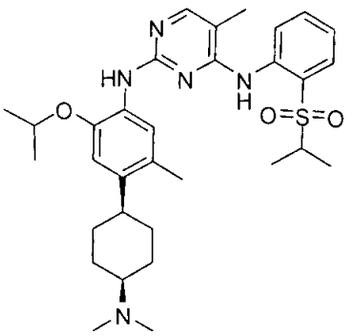
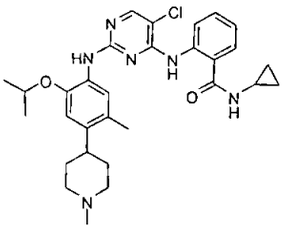
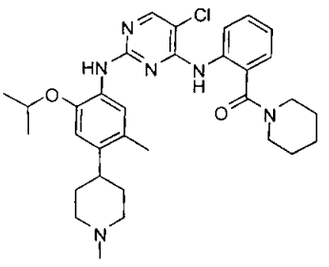
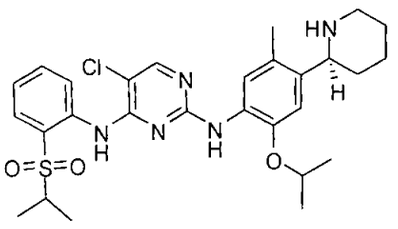
[0136] Compuestos ilustrativos de la invención se muestran a continuación. Tabla 1 muestrun compuestos ilustrativos de Fórmula (1A).

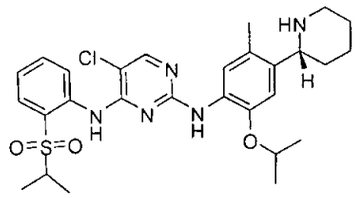
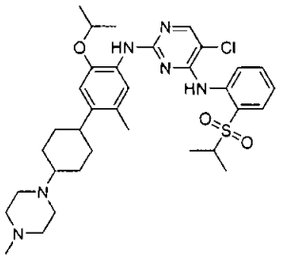
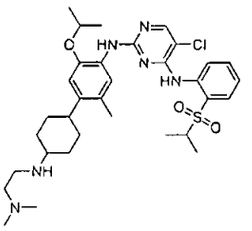
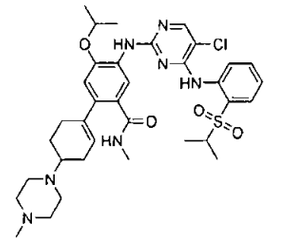
Tabla 1

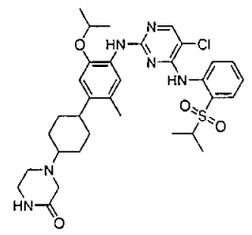
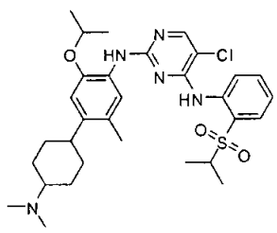
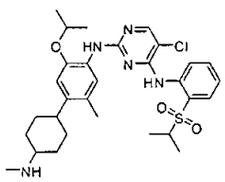
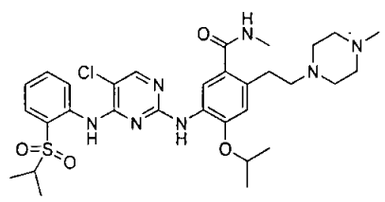
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
1	 (2-(5-cloro-2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino)pirimidin-4-ilamino)fenil)(pirrolidin-1-il)metanona	MS (ES^+): 563.1 $(M+1)^+$.
2	 2-(5-cloro-2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino)pirimidin-4-ilamino)-N-ciclopentilbenzamida	MS (ES^+): 577.2 $(M+1)^+$.
3	 N2-(4-((1R,2S,4R)-2,4-bis(dimetilamino) ciclohexil)-2-isopropoxi-5-metilfenil)-5-cloro-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES^+): 643.3 $(M+1)^+$.
4	 N2-(4-((1R,2S,4S)-2,4-bis(dimetilamino) ciclohexil)-2-isopropoxi-5-metilfenil)-5-cloro-N4-(2-	MS (ES^+): 643.3 $(M+1)^+$.

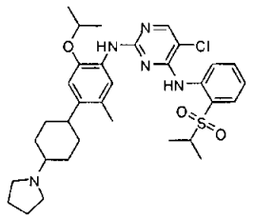
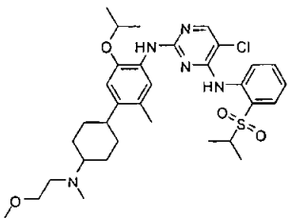
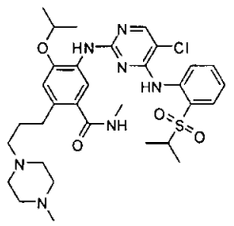
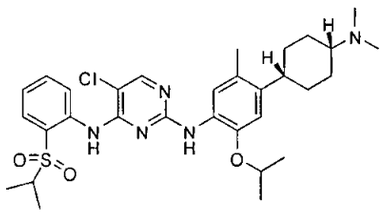
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
	(isopropilsulfonil)fenil)pirimidina-2,4-diamina	
5	 2-(5-cloro-2-(4-((1s,4s)-4-(dimetilamino) ciclohexil)-2-isopropoxi-5-metilfenilamino) pirimidin-4-ilamino)-N,Ndimetilbencenosulfonamida	MS (ES$^+$): 601.2 (M+1)$^+$.
6	 2-(5-cloro-2-(4-((1r,4r)-4-(dimetilamino)ciclohexil)-2-isopropoxi-5-metilfenilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida	MS (ES$^+$): 601.2 (M+1)$^+$.
7	 2-(5-cloro-2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino)pirimidin-4-ilamino)-N-ciclobutilbenzamida	MS (ES$^+$): 563.1 (M+1)$^+$.

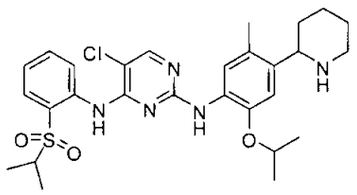
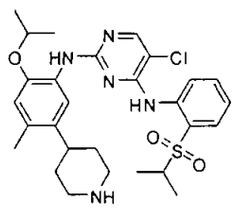
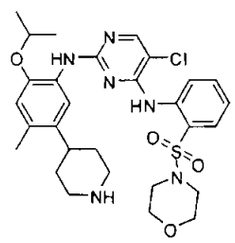
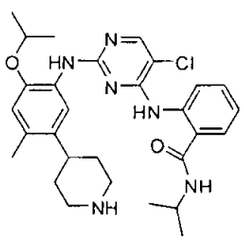
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
8	 azetidin-1-il(2-(5-cloro-2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino)pirimidin-4-ilamino)fenil)metanona	MS (ES^+): 549.1 $(M+1)^+$.
9	 5-cloro-N2-(4-((1r,4r)-4-(dimetilamino) ciclohexil)-2-isopropoxi-5-metilfenil)-N4-(2-(pirrolidin-1-ilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES^+): 627.2 $(M+1)^+$.
10	 5-cloro-N2-(4-((1s,4s)-4-(dimetilamino) ciclohexil)-2-isopropoxi-5-metilfenil)-N4-(2-(pirrolidin-1-ilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES^+): 627.2 $(M+1)^+$.
11	 N2-(4-((1r,4r)-4-(dimetilamino)ciclohexil)-2-isopropoxi-5-metilfenil)-N4-(2-(isopropilsulfonil) fenil)-5-metilpirimidina-	MS (ES^+): 580.8 $(M+1)^+$.

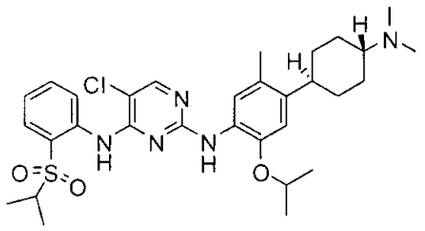
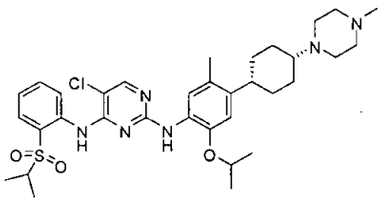
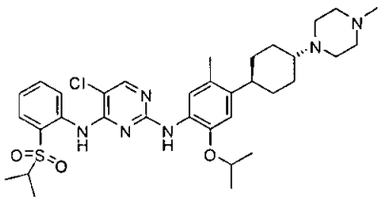
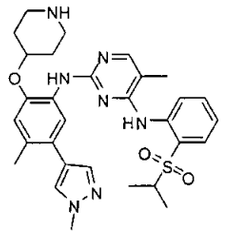
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
	2,4-diamina	
12	 N2-(4-((1s,4s)-4-(dimetilamino)ciclohexil)-2-isopropoxi-5-metilfenil)-N4-(2-(isopropilsulfonil) fenil)-5-metilpirimidina-2,4-diamina	MS (ES^+): 580.8 $(M+1)^+$.
13	 2-(5-cloro-2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino)pirimidin-4-ilamino)-N-ciclopropilbenzamida	MS (ES^+): 549.1 $(M+1)^+$.
14	 (2-(5-cloro-2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino)pirimidin-4-ilamino)fenil)(piperidin-1-il)metanona	MS (ES^+): 577.1 $(M+1)^+$.
15	 (S)-5-cloro-N2-(2-isopropoxi-5-metil-4-(piperidin-2-il)fenil)-	MS (ES^+): 558.1 $(M+1)^+$.

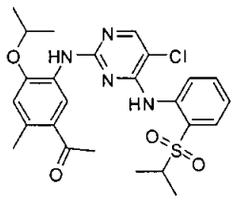
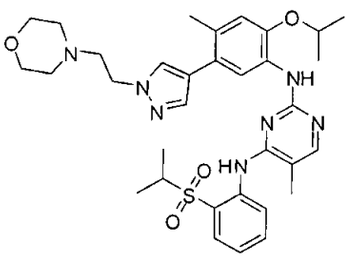
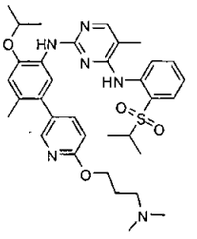
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
	N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	
16	 (R)-5-cloro-N2-(2-isopropoxi-5-metil-4-(piperidin-2-il)fenil)-N4-(2-(isopropilsulfonil)fenil) pirimidina-2,4-diamina	MS (ES^+): 558.1 $(M+1)^+$.
17	 (*cis,trans*) 5-Cloro-N2-{2-isopropoxi-5-metil-4-[4-(4-metil-piperazin-1-il)-ciclohexil]-fenil}-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina	^{1}H NMR (CD_3OD, 400 MHz) δ 8.34-8.37 (m, 1H), 8.17 (s, 1H), 7.89-7.96 (m, 1H), 7.64-7.71 (m, 1H), 7.42-7.49 (m, 2H), 6.86-6.96 (d, 1H), 4.55-4.65 (m, 1H), 3.34-3.53 (m, 1H), 2.15-2.91 (m, 12H), 1.94-1.97 (m, 4H), 1.23-1.72 (m, 20H); MS (ES^+): 654.8 $(M+1)^+$.
18	 (*cis,trans*) 5-cloro-N2-{4-[4-(2-dimetilamino-etil amino)-ciclohexil]-2-isopropoxi-5-metil-fenil}-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina	^{1}H NMR (CD_3OD, 400 MHz) δ 8.35-8.37 (d, 1H), 8.20 (s, 1H), 7.97-8.00 (m, 1H), 7.7--7.74 (m, 1H), 7.46-7.51 (m, 2H), 6.89-7.03 (d, 1H), 4.60-4.64 (m, 1H), 3.30-3.60 (m, 5H), 3.01 (s, 6H), 2.81-2.84 (m, 1H), 1.25-2.30 (m, 24H); MS (ES^+): 643.3 $(M+1)^+$.
19	 5-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-4-isopropoxi-N-metil-2-[4-(4-metil-piperazin-1-il)-ciclohex-1-enil]-benzamida	^{1}H NMR (CD_3OD, 400 MHz) δ 8.51-8.56 (t, 1H), 8.41 (s, 1H), 8.19 (s, 1H), 7.86-7.89 (m, 1H), 7.54--7.58 (m, 1H), 7.27-7.31 (m, 1H), 6.97-7.00 (m, 1H), 4.77-4.84 (m, 1H), 2.66-3.32 (m, 15H), 1.22-2.21 (m, 18H); MS (ES^+): 696.2 $(M+1)^+$.

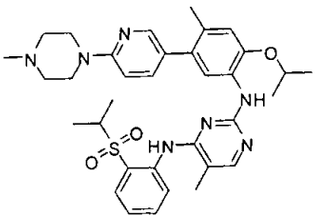
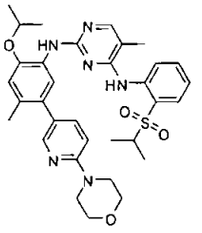
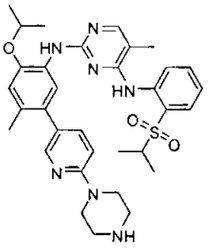
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
20	 4-[4-(4-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-metil-fenil)-ciclohexil]-piperazin-2-ona	^{1}H NMR (CD_3OD, 400 MHz) δ 8.34-8.36 (d, 1H), 8.21 (s, 1H), 7.98-8.00 (m, 1H), 7.69-7.73 (m, 1H), 7.45--7.52 (m, 2H), 6.90-7.01 (d, 1H), 4.60-4.66 (m, 1H), 3.99 (s, 2H), 3.36-3.62 (m, 6H), 1.65-2.42 (m, 12H), 1.24-1.31 (m, 12H); MS (ES^+): 655.3 $(M+1)^+$.
21	 5-Cloro-N2-[4-(4-dimetilamino-ciclohexil)-2-isopropoxi-5-metil-fenil]-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina	^{1}H NMR (CD_3OD, 400 MHz) δ 8.36-8.38 (d, 1H), 8.20 (s, 1H), 7.97-7.99 (m, 1H), 7.69-7.73 (m, 1H), 7.46--7.52 (m, 2H), 6.89-7.02 (d, 1H), 4.60-4.66 (m, 1H), 3.37-3.39 (m, 1H), 3.00 (s, 3H), 2.90 (s, 3H), 2.17-2.22 (m, 4H), 1.64-2.01 (m, 8H), 1.25-1.32 (m, 12H); MS (ES^+): 600.3 $(M+1)^+$.
22	 5-Cloro-N2-[2-isopropoxi-5-metil-4-(4-metilamino-ciclohexil)-fenil]-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina	^{1}H NMR (CD_3OD, 400 MHz) δ 8.32-8.34 (d, 1H), 8.22 (s, 1H), 7.98-8.00 (m, 1H), 7.69-7.73 (m, 1H), 7.49--7.53 (m, 1H), 7.40-7.41 (d, 1H), 6.91-7.02 (d, 1H), 4.61-4.66 (m, 1H), 3.36-3.40 (m, 1H), 2.74-2.78 (d, 3H), 2.17-2.28 (m, 4H), 1.64-2.03 (m, 8H), 1.24-1.31 (m, 12H); MS (ES^+): 586.2 $(M+1)^+$.
23	 5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metil-2-(2-(4-metilpiperazin-1-il)etil)benzamida	MS (ES^+): 645.2 $(M+1)^+$

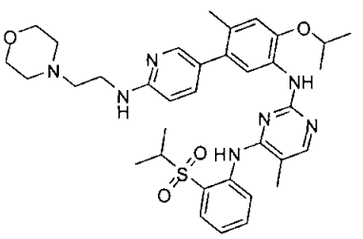
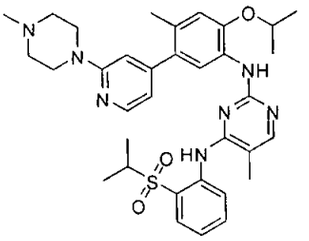
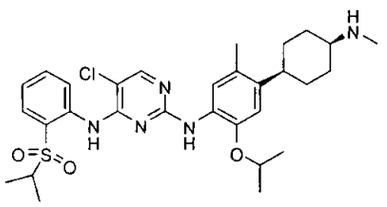
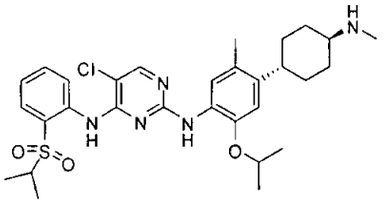
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
24	 5-Cloro-N2-[2-isopropoxi-5-metil-4-(4-pirrolidin-1-il-ciclohexil)-fenil]-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina	^{1}H NMR (CD_3OD, 400 MHz) δ 8.36-8.38 (d, 1H), 8.20 (s, 1H), 7.97-7.99 (m, 1H), 7.69-7.73 (m, 1H), 7.45--7.52 (m, 2H), 6.88-7.02 (d, 1H), 4.60-4.66 (m, 1H), 3.65-3.85 (m, 2H), 3.32-3.34 (m, 1H), 3.16-3.20 (m, 2H), 2.77-2.96 (m, 1H), 1.22-2.35 (m, 28H); MS (ES^+): 626.3 $(M+1)^+$.
25	 5-Cloro-N2-(2-isopropoxi-4-{4-[(2-metoxi-etil)-metil-amino]-ciclohexil}-5-metil-fenil)-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina	^{1}H NMR (CD_3OD, 400 MHz) δ 8.36-8.38 (d, 1H), 8.20-8.21 (m, 1H), 7.96-7.99 (m, 1H), 7.69-7.73 (m, 1H), 7.45--7.54 (m, 2H), 6.90-7.02 (d, 1H), 4.60-4.66 (m, 1H), 3.32-3.77 (m, 8H), 2.90-2.99 (m, 3H), 2.77-2.96 (m, 1H), 1.22-2.33 (m, 24H); MS (ES^+): 644.3 $(M+1)^+$.
26	 5-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-4-isopropoxi-N-metil-2-[3-(4-metil-piperazin-1-il)-propil]-benzamida	^{1}H NMR (CD_3OD, 400 MHz) δ 8.44-8.46 (d, 1H), 8.25 (s, 1H), 8.13 (s, 1H), 7.94-7.96 (m, 1H), 7.64-7.67 (m, 1H), 7.42--7.46 (m, 1H), 7.06 (s, 1H), 4.77-4.83 (m, 1H), 3.48-3.54 (m, 8H), 3.32-3.35 (m, 1H), 3.06-3.10 (m, 2H), 2.96 (s, 3H), 2.81-2.87 (m, 5H), 2.16-2.20 (m, 2H), 1.27-1.39 (m, 12H); MS (ES^+): 658.3 $(M+1)^+$.
27	 5-cloro-N2-(4-((1s,4s)-4-(dimetilamino) ciclohexil)-2-isopropoxi-5-metilfenil)-N4-(2-	MS (ES^+): 600.2 $(M+1)^+$.

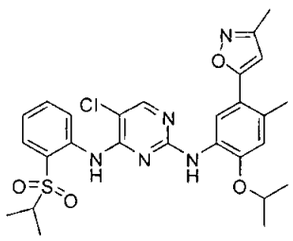
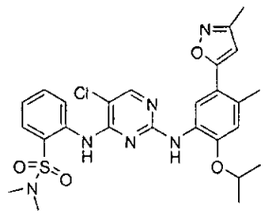
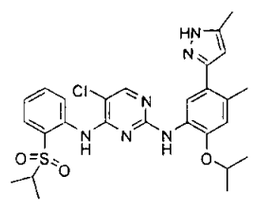
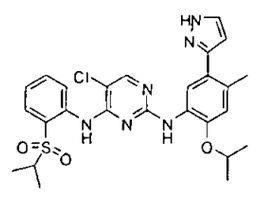
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
	(isopropilsulfonil)fenil)pirimidina-2,4-diamina	
28	 5-cloro-N2-(2-isopropoxi-5-metil-4-(piperidin-2-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES^+): 558.2 $(M+1)^+$.
29	 5-cloro-N2-(2-isopropoxi-4-metil-5-(piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil) pirimidina-2,4-diamina	MS (ES^+): 558.2 $(M+1)^+$.
30	 5-cloro-N2-(2-isopropoxi-4-metil-5-(piperidin-4-il)fenil)-N4-(2(morfolinosulfonamido) fenil)pirimidina-2,4-diamina	MS (ES^+): 601.2 $(M+1)^+$.
31	 2-(2-(2-isopropoxi-4-metil-5-(piperidin-4-il)fenilamino)-5-cloropirimidin-4-ilamino)-N-isopropilbenzamida	MS (ES^+): 537.3 $(M+1)^+$.

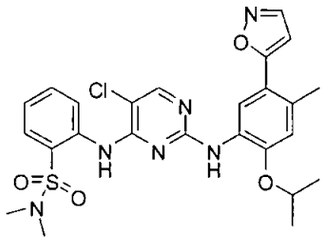
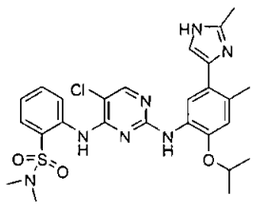
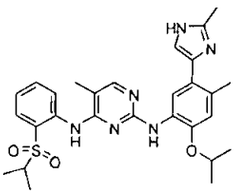
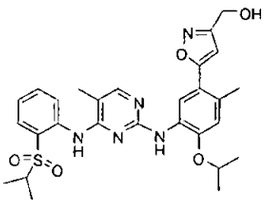
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
32	 5-cloro-N2-(4-((1r,4r)-4-(dimetilamino) ciclohexil)-2-isopropoxi-5-metilfenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES^+): 600.3 $(M+1)^+$.
33	 5-cloro-N2-(2-isopropoxi-5-metil-4-((1s,4s)-4-(4-metilpiperazin-1-il)ciclohexil)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES^+): 655.3 $(M+1)^+$.
34	 5-cloro-N2-(2-isopropoxi-5-metil-4-((1r,4r)-4-(4-metilpiperazin-1-il)ciclohexil)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES^+): 655.3 $(M+1)^+$.
35	 5-Metil-N2-[4-metil-5-(1-metil-1H-pirazol-4-il)-2-(piperidin-4-iloxi)-fenil]-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina	1.10 (6H, d, J=5.7), 1.89 (2H, br), 2.03 (2H, br), 2.16 (3H, s), 2.32 (3H, s), 3.05 (2H, br), 3.49 (3H, br), 3.89 (3H, s), 4.72 (1H, br), 7.06 (1H, s), 7.21 (1H, br), 7.30 (1H, br), 7.41 (1H, br.s), 7.46 (1H, br.s), 7.69 (1H, s), 7.79 (1H, d, J= 7.4), 7.95 (1H, br), 8.04 (1H, br.s), 9.79 (2H, br.s). MS (ES^+): 576.3 $(M+1)^+$.

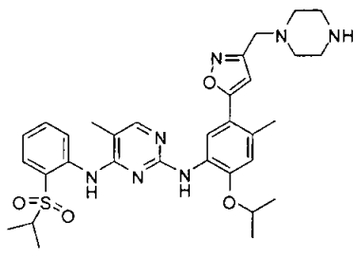
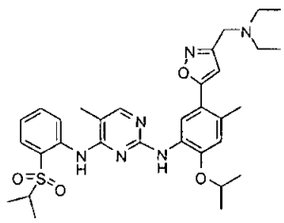
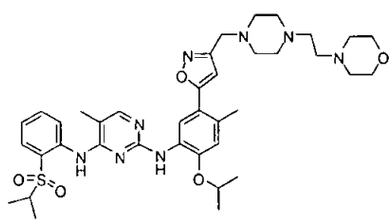
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
36	 1-(5-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-4-isopropoxi-2-metil-fenil)-etanona	1.10 (6H, d, J=5.7), 1.89 (2H, br), 2.03 (2H, br), 2.16 (3H, s), 2.32 (3H, s), 3.05 (2H, br), 3.49 (3H, br), 3.89 (3H, s), 4.72 (1H, br), 7.06 (1H, s), 7.21 (1H, br), 7.30 (1H, br), 7.41 (1H, br.s), 7.46 (1H, br.s), 7.69 (1H, s), 7.79 (1H, d, J= 7.4), 7.95 (1H, br), 8.04 (1H, br.s), 9.79 (2H, br.s). MS (ES^+): 517.2 $(M+1)^+$.
37	 N2-{2-Isopropoxi-4-metil-5-[1-(2-morfolin-4-il-etil)-1H-pirazol-4-il]-fenil}-5-metil-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina	1.14 (6H, d, J=6.8), 1.25 (6H, d, J=6.0), 2.12 (3H, s), 2.33 (3H, s), 2.52 (sobrelapping con DMSO), 3.14 (2H, very br.) 3.45 (1H, sept, J=6.8), 3.70 (4H, very br), 3.93 (2H, very br), 4.6 (1 o 2H, br.S), 4.63 (1H, sept, J= 6.1), 6.99 (1H, s), 7.23 (2H, m), 7.53 (1H, s), 7.78 (2H, m)7.91 (1H, s), 8.01 (1H, s), 8.33 (1H, br.s), missing anilino NH. MS (ES^+): 634.3 $(M+1)^+$.
38	 N2-(5-(6-(3-(dimetilamino)propoxi)piridin-3-il)-2-isopropoxi-4-metilfenil)-N4-(2-(isopropil sulfonil)fenil)-5-metilpirimidina-2,4-diamina	1.06 (6H, d, J=6.7), 1.28 (6H, d, J=6.0), 2.15 (6H, s), 2.19 (2H, br.m), 2.80 (3H, s), 2.82 (3H, s), 3.25 (2H, m), 3.39 (1H, m), 4.39 (2H, t, J=6.1), 4.70 (1H, sept, J=6.1), 6.86 (1H, d, J=8.5), 7.07 (1H, s), 7.19 (1H, br.s), 7.35 (2H, br.s), 7.48 (1H, br.m)7.74 (1H, br.d, J=6.4), 7.84 (2H, br.s), 8.05 (1H, br.s), 9.76 (1H, s), 10.15 (1H, br.s). MS (ES^+): 633.8 $(M+1)^+$.

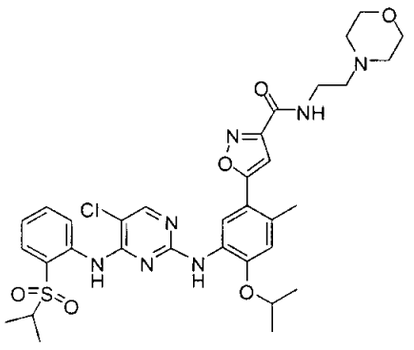
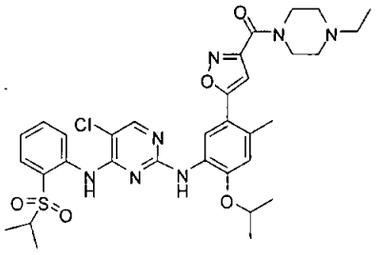
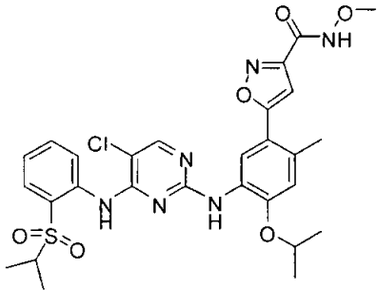
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
39	 N2-(2-isopropoxi-4-metil-5-(6-(4-metilpiperazin-1-il)piridin-3-il)fenil)-N4-(2-(isopropilsulfonil) fenil)-5-metilpirimidina-2,4-diamina	1.06 (6H, d, J=6.7), 1.28 (6H, d, J=6.0), 2.15 (6H, s), 2.19 (2H, br.m), 2.80 (3H, s), 2.82 (3H, s), 3.25 (2H, m), 3.39 (1H, m), 4.39 (2H, t, J=6.1), 4.70 (1H, sept, J=6.1), 6.86 (1H, d, J=8.5), 7.07 (1H, s), 7.19 (1H, br.s), 7.35 (2H, br.s), 7.48 (1H, br.m)7.74 (1H, br.d, J=6.4), 7.84 (2H, br.s), 8.05 (1H, br.s), 9.76 (1H, s), 10.15 (1H, br.s). MS (ES^+): 630.8 $(M+1)^+$.
40	 N2-(2-isopropoxi-4-metil-5-(6-morfolinopiridin-3-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-5-metilpirimidina-2,4-diamina	1.08 (6H, d, J=6.7), 1.28 (6H, d, J=6.0), 2.15 (3H, s), 2.19 (3H, s), 3.59 (4H, br), 3.78 (4H, br), 4.70 (1H, sept, J=6.1), 7.02 (1H, br.s), 7.07 (1H, s),7.24 (1H, br.s), 7.35 (2H, br.s). 7.49 (1H, br.s), 7.75 (1H, br.d, J=6.8), 7.81 (1H, br.s), 7.86 (1H, br), 8.04 (1H, br.s), 9.76 (1H, br.s). MS (ES^+): 617.8 $(M+1)^+$.
41	 N2-(2-isopropoxi-4-metil-5-(6-(piperazin-1-il)piridin-3-il)fenil)-N4-(2-(isopropilsulfonil) fenil)-5-metilpirimidina-2,4-diamina	1.12 (6H, d, J=6.7), 1.31 (6H, d, J=6.0), 2.09 (3H, s), 2.18 (3H,s), 3.25 (4H, br.s), 3.39 (1H, sept, J=6.8), 3.75 (4H, br.t, J=5.1), 4.68 (1H, sept, J=6.1), 6.90 (1H, d, J=9.0), 6.98 (1H, s), 7.01 (1H, br.s), 7.11 (1H, br.s), 7.44 (1H, s), 7.47 (1H,s) 7.70 (1H, d, J=7.7), 7.92 (1H, s) 8.04 (1H, s), 8.23 (1H, br.s), 8.90 (1H, br.s), 8.94 (1H, br.s). MS (ES^+): 616.8 $(M+1)^+$.

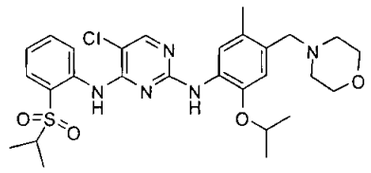
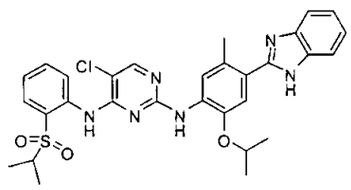
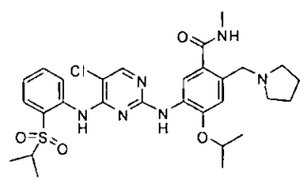
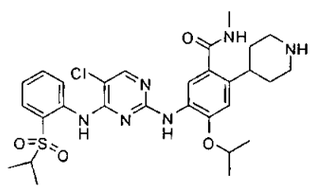
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
42	 N2-(5-(6-(2-morfolinoetilamino)piridin-3-il)-2-isopropoxi-4-metilfenil)-N4-(2-(isopropil-sulfonil)fenil)-5-metilpirimidina-2,4-diamina	MS (ES^+): 660.8 $(M+1)^+$.
43	 N2-(2-isopropoxi-4-metil-5-(2-(4-metilpiperazin-1-il)piridin-4-il)fenil)-N4-(2-(isopropilsulfonil) fenil)-5-metilpirimidina-2,4-diamina	1.13 (6H, d, J=6.8), 1.32 (6H, d, 6.0), 20.9 (3H, s), 2.20 (3H, s), 2.76 (3H, br.s), 3.1 (4H, very br.), 3.38 (H_2O sobrelap), 3.40 (1H, sept, J=6.8), 4.36 (1H, very br), 4.70 (1H, sept, J=6.0), 6.60 (1H, d, J=4.7), 6.73 (1H, s), 7.00 (3h, br) 7.68 (1H, s), 7.72 (1H, dd, J=1.8, 7.5), 7.95 (1H, s), 8.03 (1H, s), 8.12 (1H, d, J=5.1), 8.31 (1H, br.d, J=7.6), 8.91 (1H, s). 630.8 $(M+1)^+$.
44	 5-cloro-N2-(2-isopropoxi-5-metil-4-((1s,4s)-4-(metilamino)ciclohexil)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES^+): 586.3 $(M+1)^+$
45	 5-cloro-N2-(2-isopropoxi-5-metil-4-((1r,4r)-4-(metilamino)ciclohexil)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES^+): 586.3 $(M+1)^+$

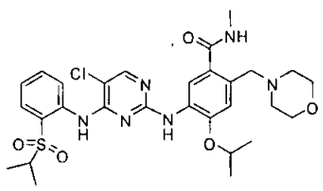
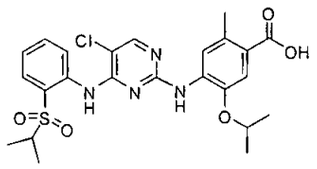
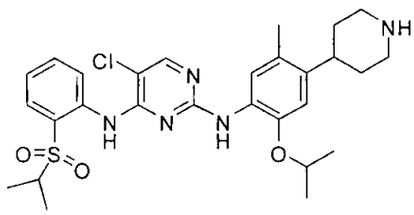
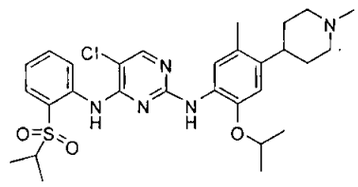
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
46	 5-cloro-N2-(2-isopropoxi-4-metil-5-(3-metilisoxazol-5-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	1H NMR (400 MHz, MeOD-d4) δ 8.15 (1H, s), 8.12 (1H, d, *J* = 7.6 Hz), 7.93 (1H, s), 7.78 (1H, d, *J* = 7.6 Hz), 7.20 (2H, m), 6.96 (1H, s), 6.18 (1H, s), 4.68 (1H, m), 3.28 (1H, m), 2.38 (3H, s), 2.23 (3H, s), 1.26 (6H, d, *J* = 6.0Hz), 1.16 (6H, d, *J* = 6.8 Hz) .MS (ES^+): 556.2 $(M+1)^+$.
47	 2-(5-cloro-2-(2-isopropoxi-4-metil-5-(3-metilisoxazol-5-il)fenilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida	1H NMR (400 MHz, MeOD-d4) δ 8.20 (1H, s), 8.12 (1H, d, *J* = 7.6 Hz), 7.97 (1H, s), 7.78 (1H, d, *J* = 7.6 Hz), 7.20 (2H, m), 7.01 (1H, s), 6.24 (1H, s), 4.74 (1H, m), 2.68 (6H, s), 2.43 (3H, s), 2.29 (3H,s), 1.32 (6H, d, *J* = 6.0 Hz).MS (ES^+): 557.2 $(M+1)^+$.
48	 5-cloro-N2-(2-isopropoxi-4-metil-5-(5-metil-1H-pirazol-3-il)fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina	1H NMR (400 MHz, MeOD-d4) δ 8.29 (1H, s), 8.13 (1H, bs), 7.97 (1H, s), 7.87 (1H, d, *J* = 7.6 Hz), 7.75 (1H, s), 7.35 (2H, m), 7.09 (1H,s), 6.41 (1H, s), 4.80 (1H, m), 3.40 (1H, m), 2.50 (3H, s), 2.40 (3H, s), 1.36 (6H, d, *J* = 6.0 Hz), 1.25 (3H, d, *J* = 6.8 Hz). MS (ES^+): 555.2 $(M+1)^+$.
49	 5-cloro-N2-(2-isopropoxi-4-metil-5-(1H-pirazol-3-il)fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina	1H NMR (400 MHz, MeOD-d4) δ 8.27 (1H, s), 8.20 (1H, bs), 7.90 (1H, d, *J* = 6.4 Hz), 7.81 (1H, bs), 7.67 (1H, s), 7.37 (2H, bs), 7.08 (1H,s), 6.45 (1H, s), 4.76 (1H, m), 3.38 (1H, m), 2.41 (3H, s), 1.35 (6H, d, *J* = 6.0 Hz), 1.25 (3H, d, *J* = 6.8 Hz).MS (ES^+): 541.2 $(M+1)^+$.

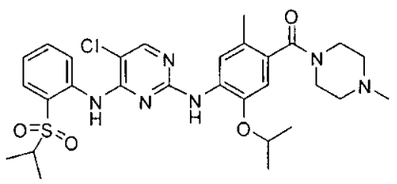
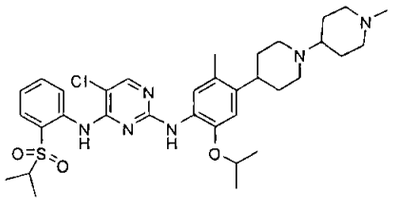
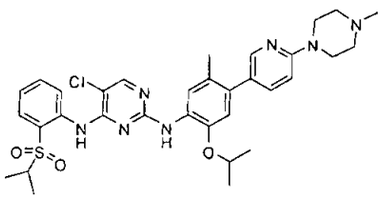
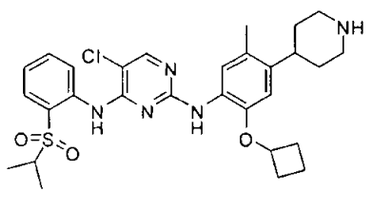
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
50	 2-(5-cloro-2-(2-isopropoxi-5-(isoxazol-5-il)-4-metilfenilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida	1H NMR (400 MHz, MeOD-d4) δ 8.31 (1H, s), 8.16 (1H, s), 8.03 (1H, bs), 7.92 (1H, s), 7.74 (1H, d, *J* = 7.2 Hz), 7.17 (2H, bs), 6.99 (1H,s), 6.34 (1H, s), 4.69 (1H, m), 2.64 (6H, s), 2.39 (3H, s), 1.27 (6H, d, *J* = 6.0 Hz). MS (ES^+): 543.2 $(M+1)^+$.
51	 2-(5-cloro-2-(2-isopropoxi-4-metil-5-(2-metil-1H-imidazol-4-il)fenilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida	1H NMR (400 MHz, MeOD-d4) δ 8.18 (1H, s), 7.94 (1H, d, *J* = 5.2 Hz), 7.72 (1H, s), 7.70 (1H, s), 7.29 (2H, bs), 7.21 (2H, bs), 7.00 (1H,s), 4.68 (1H, m), 2.65 (6H, s), 2.58 (3H, s), 2.28 (3H, s), 1.27 (6H, d, *J* = 6.0 Hz). .MS (ES^+): 556.2 $(M+1)^+$.
52	 5-cloro-N2-(2-isopropoxi-4-metil-5-(2-metil-1H-imidazol-4-il)fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina	1H NMR (400 MHz, MeOD-d4) δ 8.10 (1H, bs), 7.90 (1H, s), 7.85 (1H, d, *J* = 7.6 Hz), 7.65 (1H, s), 7.48 (1H, bs), 7.36 (2H, bs), 7.12 (1H,s), 4.70 (1H, m), 3.39 (1H, m), 2.70 (3H, s), 2.40 (3H, s), 2.26 (3H, s), 1.34 (6H, d, *J* = 6.0 Hz), 1.24 (6H, d, *J* = 6.8 Hz). MS (ES^+): 535.2 $(M+1)^+$.
53	 (5-(5-(4-(2-(isopropilsulfonil)fenilamino)-5-metilpirimidin-2-ilamino)-4-isopropoxi-2-metilfenil)isoxazol-3-il)metanol	1H NMR (400 MHz, MeOD-d4) δ 8.39 (1H, s), 8.31 (1H, d, *J* = 8.0 Hz), 7.98 (1H, s), 7.81 (1H, d, *J* = 7.2 Hz), 7.19 (1H, bs), 7.10 (1H, bs), 6.97 (1H, s), 6.29 (1H,s), 4.78 (1H, m), 4.66 (2H, s), 3.39 (1H, m), 2.44 (3H, s), 2.18 (3H, s), 2.26 (3H, s), 1.41 (6H, d, *J* = 5.6 Hz), 1.27 (6H, d, *J* = 6.8 Hz). MS (ES^+): 552.6

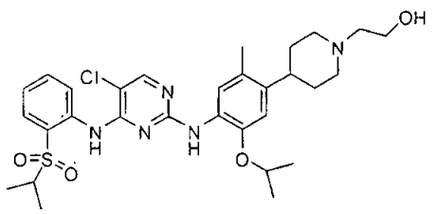
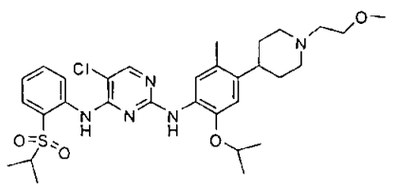
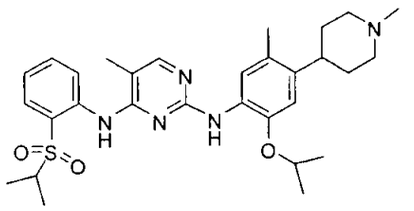
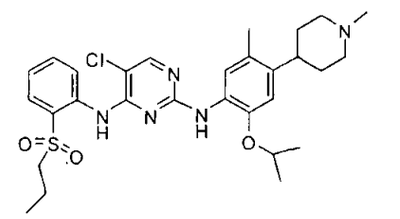
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
		$(M+1)^+$.
54	 N2-(2-isopropoxi-4-metil-5-(3-((piperazin-1-il)metil)isoxazol-5-il)fenil)-N4-(2-(isopropil-sulfonil)fenil)-5-metilpirimidina-2,4-diamina	1H NMR (400 MHz, MeOD-d4) δ 8.31 (1H, d, J = 8.4 Hz), 8.29 (1H, s), 7.88 (1H, s), 7.71 (1H, d, J = 8.0 Hz), 7.11 (1H, t, J = 8.8 Hz), 6.98 (1H, t, J = 7.2 Hz), 6.88 (1H, s), 6.25 (1H,s), 4.67 (1H, m), 3.59 (2H, s), 3.22 (1H, m), 3.03 (4H, bs), 2.61 (4H, bs), 2.35 (3H, s), 2.07 (3H, s), 1.30 (6H, d, J = 5.6 Hz), 1.17 (6H, d, J = 6.8 Hz)..MS (ES^+): 620.8 $(M+1)^+$.
55	 N2-(5-(3-((dietilamino)metil)isoxazol-5-il)-2-isopropoxi-4-metilfenil)-N4-(2-(isopropil-sulfonil)fenil)-5-metilpirimidina-2,4-diamina	1H NMR (400 MHz, MeOD-d4) δ 8.35 (1H, s), 8.33 (1H, d, J = 8.4 Hz), 7.89 (1H, s), 7.72 (1H, d, J = 8.0 Hz), 7.15 (1H, t, J = 8.8 Hz), 7.01 (1H, t, J = 7.2 Hz), 6.90 (1H, s), 6.47 (1H,s), 4.69 (1H, m), 4.19 (2H, s), 3.24 (1H, m), 3.00 (4H, bs), 2.38 (3H, s), 2.08 (3H, s), 1.22 (6H, t, J = 7.2 Hz), 1.17 (6H, d, J = 6.8 Hz). MS (ES^+): 607.8 $(M+1)^+$.
56	 N2-(2-isopropoxi-4-metil-5-(3-((4-(2-morfolinoetil)piperazin-1-il)metil)isoxazol-5-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-5-metilpirimidina-2,4-diamina	1H NMR (400 MHz, MeOD-d4) δ 8.31 (1H, d, J = 8.4 Hz), 8.28 (1H, s), 7.87 (1H, s), 7.70 (1H, d, J = 8.0 Hz), 7.08 (1H, t, J = 8.8 Hz), 6.99 (1H, t, J = 7.2 Hz), 6.87 (1H, s), 6.25 (1H,s), 4.66 (1H, m), 3.61 (4H, m), 3.55 (2H, s), 3.21 (1H, m), 2.34-2.59 (12H, m), 2.35 (3H, s), 2.06 (3H, s), 1.29 (6H, d, J = 6.0 Hz), 1.16 (6H, d, J = 6.8 Hz). MS (ES^+): 733.4 $(M+1)^+$.

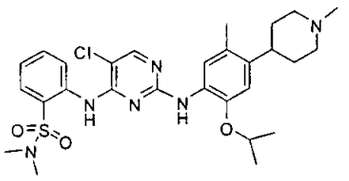
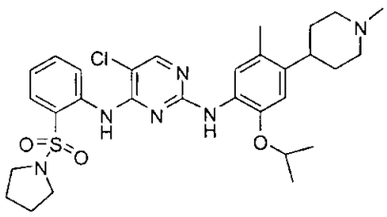
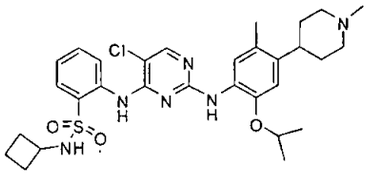
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
57	 5-(5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-2-metilfenil)-N-(2-morfolinoetil)isoxazol-3-carboxamida	1H NMR (400 MHz, MeOD-d4) δ 8.33 (1H, s), 8.17 (1H, bs), 7.93 (1H, s), 7.92 (1H, d, *J* = 7.2 Hz), 7.91 (1H, s), 7.37-7.39 (2H, m), 7.17 (1H, s), 6.83 (1H, s), 4.84 (1H, m), 4.11 (2H, dd, *J* = 2.8 y 12.8 Hz) 3.83-3.88 (4H, m), 3.70 (2H, d, *J* = 12.4 Hz), 3.42-3.48 (3H, m), 3.21 (2H, m), 2.54 (3H, s), 1.36 (6H, d, *J* = 6.0 Hz), 1.26 (6H, d, *J* = 6.8 Hz). MS (ES^+): 698.2 $(M+1)^+$.
58	 (5-(5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-2-metilfenil)isoxazol-3-il)(4-etilpiperazin-1-il)metanona	1H NMR (400 MHz, MeOD-d4) δ 8.33 (1H, s), 8.12 (1H, bs), 7.93 (1H, s), 7.95 (1H, s), 7.91 (1H, d, *J* = 8.8 Hz), 7.35-7.44 (2H, m), 7.15 (1H, s), 6.76 (1H, s), 4.85 (1H, m), 3.66-3.76 (4H, m) 3.38-3.43 (2H, m), 3.10 (2H, m), 2.54 (3H, s), 1.42 (3H, t, *J* = 7.2 Hz), 1.37 (6H, d, *J* = 6.0 Hz), 1.27 (6H, d, *J* = 6.8 Hz). MS (ES^+): 682.3 $(M+1)^+$.
59	 5-(5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-2-metilfenil)-N-metoxiisoxazol-3-carboxamida	1H NMR (400 MHz, MeOD-d4) δ 8.17 (1H, s), 8.06 (1H, d, *J* = 8.0 Hz), 8.02 (1H, s), 7.77 (1H, d, *J* = 7.6 Hz), 7.21 (1H, bs), 7.12 (1H, t, *J* = 7.6 Hz), 6.97 (1H, s), 6.51 (1H, s), 4.71 (1H, m), 3.77 (3H, s), 3.29 (1H, m), 2.39 (3H, s), 1.28 (6H, d, *J* = 6.0 Hz), 1.17 (6H, d, *J* = 6.8 Hz). MS (ES^+): 615.1 $(M+1)^+$.

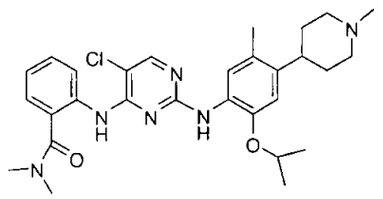
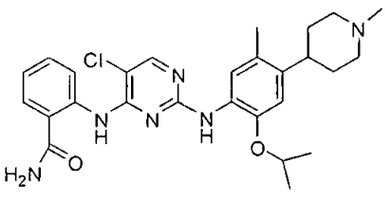
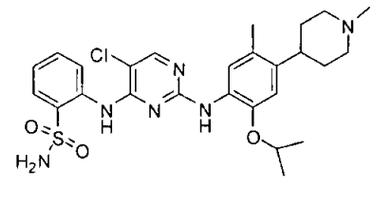
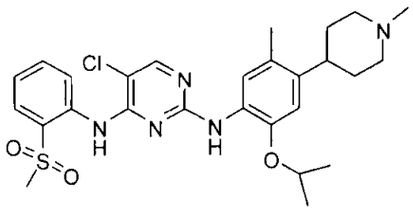
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
60	 5-Cloro-N2-(2-isopropoxi-5-metil-4-morfolin-4-ilmetil-fenil)-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina	1H NMR (400 MHz, CDCl3) 10.35(s, 1H), 8.38 (d, 1H0, 7.93 (d, 1H), 7.59 (m, 2H), 7.41-7.36 (m, 2H), 4.70-4.63(br, 1H), 4.30-4.18 (br, 2H), 4.15-4.10 (br, 2H), 4.00-3.97 (br, 2H), 3.52-3.46 (br, 2H), 3.20 (m, 1H), 2.95-2.84 (br, 2H), 2.24 (s, 3H), 1.31 (d, 12H). MS (ES^+): 574.2 $(M+1)^+$.
61	 N2-(4-(1H-benzo[d]imidazol-2-il)-2-isopropoxi-5-metilfenil)-5-cloro-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	1H NMR (400 MHz, CDCl3) 10.43 (s, 1H), 9.68 (s, 1H), 8.32 (d, 1H), 8.04 (s, 1H), 7.93 (d, 1H), 7.71-7.65 (m, 3H), 7.59 (s, 1H), 7.40-7.37 (, 3H), 4.46-4.43 (m, 1H), 3.31-3.20 (m, 1H), 2.38 (s, 3H), 1.32 (d, 6H), 1.15 (d, 6H). MS (ES^+): 591.2 $(M+1)^+$.
62	 5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metil-2-((pirrolidin-1-il)metil)benzamida	MS (ES^+): 601.2 $(M+1)^+$.
63	 5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metil-2-(piperidin-4-il)benzamida	1H NMR: (DMSO-d6 + trace D2O): δ 8.46(d,1H);8.30(s,1H); 7.83(s,1H);7.81(s,1H);7.58(t,1); 7.33(t,1H);6.88(s,1H);4.65(m,1H);3.37(m,1H);3.35 (d,2H); 3.18 (m,1H); 2.98(m,2H); 2.65 (s,3H); 1.90(d,2H); 1.84(m,2H);1,28 (d,6H);1.17(d,6H). MS (ES^+): 602.2 $(M+1)^+$.

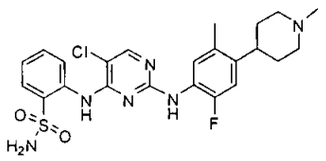
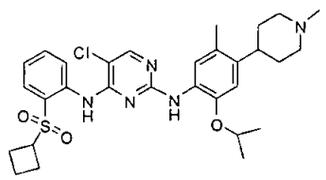
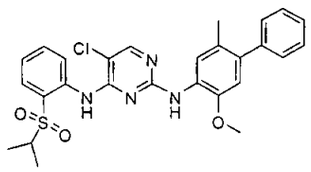
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
64	 5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metil-2-(morfolinometil)benzamida	1H NMR: (DMSO-d6 + trace D2O): δ 8.48(d,1H);8.36(s,1H); 8.27(s,1H); 7.82(dd,1H); 7.52 (m,1H); 7.36(d,1H); 7.33(s,1H); 4.76(m,1H); 4.39 (s, 2H); 4.01 (d,2H); 3.70(t,2H); 3.44 (m,1H); 3.36(d,2H); 3.19 (t,2H); 2.66(s, 3H);1.30(d,6H); 1.18(d,6H).MS (ES^+): 617.2 $(M+1)^+$.
65	 4-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-metilbenzóico ácido	(TFA sal, CD3OD) δ 8.44 (d, 1H), 8.31 (s, 1H), 8.09 (s, 1H), 7.98 (d, 1H), 7.80 (dd, 1H), 7.59 (s, 1H), 7.45 (dd, 1H), 4.75-4.65 (m, 1H), 3.40-3.30 (m, 1H, parcialmente obscured by CD3OD peak), 2.36 (s, 3H), 1.41 (d, 6H), 1.31 (d, 6H). MS (ES^+): 519.1 $(M+1)^+$.
66	 5-cloro-N2-(2-isopropoxi-5-metil-4-(piperidin-4-il)fenil)-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina	(HCl sal, DMSO-d6 + trace D2O) δ 8.32 (s, 1H), 8.27 (d, 1H), 7.88 (d, 1H), 7.67 (dd, 1H), 7.45 (dd, 1H), 7.42 (s, 1H), 6.79 (s, 1H), 4.56-4.48 (m, 1H), 3.49-3.32 (m, 3H), 3.10-2.91 (m, 3H), 2.09 (s, 3H), 1.89-1.77 (m, 4H), 1.22 (d, 6H), 1.13 (d, 6H). MS (ES^+): 558.1 $(M+1)^+$.
67	 5-cloro-N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-[2-(propano-2-sulfonil)fenil]-pirimidina-2,4-diamina	(HCl sal, DMSO-d6 + trace D2O) δ 8.28 (s, 1H), 8.19 (d, 1H), 7.86 (d, 1H), 7.66 (dd, 1H), 7.45 (dd, 1H), 7.37 (s, 1H), 6.77 (s, 1H), 4.56-4.49 (m, 1H), 3.51-3.37 (m, 3H), 3.16-3.08 (m, 2H), 2.98-2.88 (m, 1H), 2.77 (s, 3H), 2.05 (s, 3H), 1.90-1.81 (m, 4H), 1.19 (d, 6H), 1.11 (d, 6H). MS

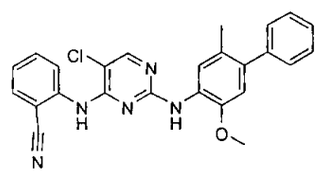
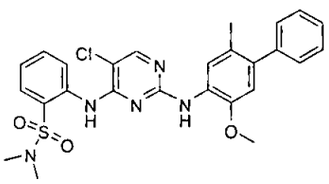
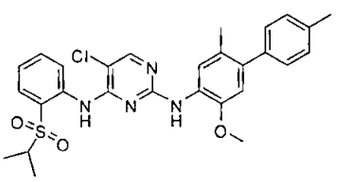
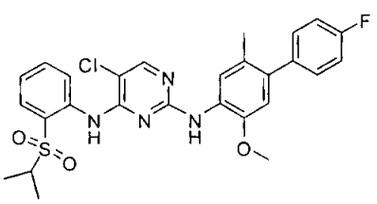
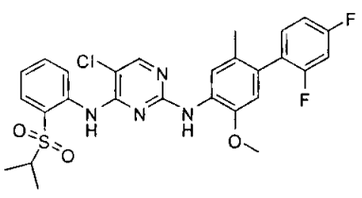
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
		(ES$^+$): 572.2 $(M+1)^+$.
68	 (4-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-metilfenil)(4-metilpiperazin-1-il)metanona	MS (ES$^+$): 601.2 $(M+1)^+$.
69	 5-cloro-N2-(2-isopropoxi-5-metil-4-(1-(1-metilpiperidin-4-il)piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES$^+$): 655.3 $(M+1)^+$.
70	 5-cloro-N2-(2-isopropoxi-5-metil-4-(6-(4-metilpiperazin-1-il)piridin-3-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES$^+$): 650.3 $(M+1)^+$.
71	 5-cloro-N2-(2-ciclobutoxi-5-metil-4-(piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina	MS (ES$^+$): 570.2 $(M+1)^+$.

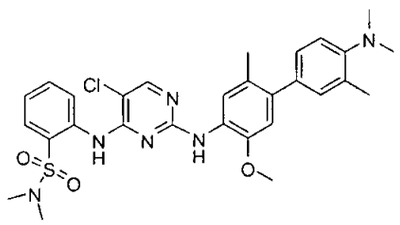
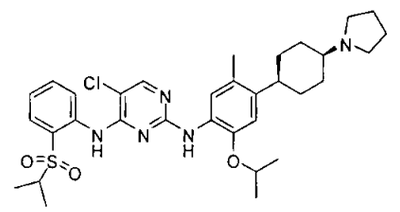
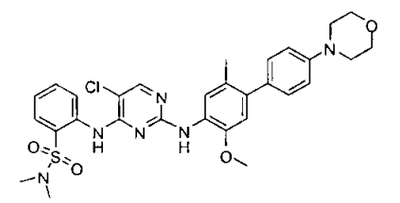
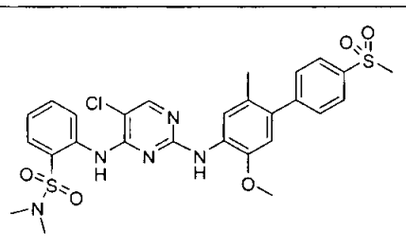
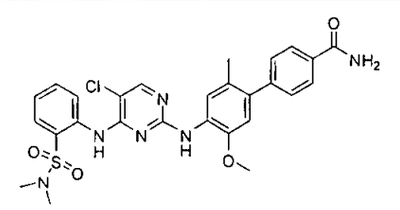
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
72	 2-[4-(4-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-metil-fenil)-piperidin-1-il]-etanol	MS (ES^+): 602.2 $(M+1)^+$.
73	 5-cloro-N2-(2-isopropoxi-4-(1-(2-metoxietil)piperidin-4-il)-5-metilfenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES^+): 616.3 $(M+1)^+$.
74	 N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-5-metilpirimidina-2,4-diamina	^{1}H NMR (HCl sal, DMSO-d6 + trace D2O, 400 MHz) 8.04 (s, 1H), 7.96 (dd, J = 8.0, 1.6 Hz, 2H), 7.79 (m, 1H), 7.61 (m, 1H), 7.27 (s, 1H), 6.81 (s, 1H), 4.55 (m, 1H), 3.43 (m, 3H), 3.08 (m, 2H), 2.91 (m, 1H), 2.77 (s, 3H), 2.17 (s, 3H), 1.98 (s, 3H), 1.91 (m, 2H), 1.80 (m, 2H), 1.24 (d, J = 6.0 Hz, 6H), 1.10 (d, J = 6.8 Hz, 6H). MS (ES^+): 552.7 $(M+1)^+$.
75	 5-cloro-N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(propilsulfonil)fenil)pirimidina-2,4-diamina	^{1}H NMR (HCl sal, CD_3OD, 400 MHz) 8.15 (s, 1H), 8.05 (m, 1H), 7.94 (dd, J = 8.0, 1.2 Hz, 1H), 7.66 (m, 1H), 7.50 (m, 1H), 7.19 (s, 1H), 6.83 (s, 1H), 4.60 (m, 1H), 3.54 (m, 2H), 3.13 (m, 4H), 2.99 (m, 1H), 2.82 (s, 3H), 2.06 (s, 3H), 1.91 (m, 4H), 1.54 (m, 2H), 1.19 (d, J = 2.0 Hz,

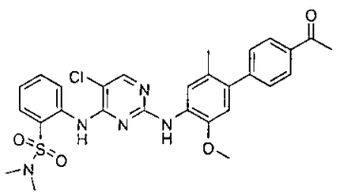
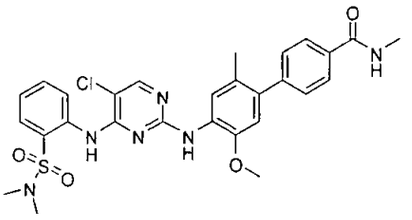
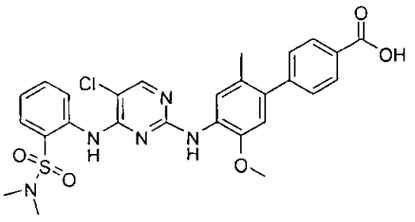
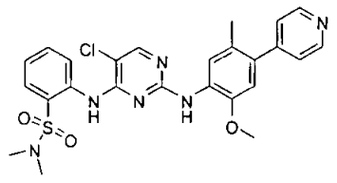
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
		6H), 0.82 (t, *J* = 7.6 Hz, 3H). MS (ES^+): 572.2 $(M+1)^+$.MS (ES^+): 572.2 $(M+1)^+$.
76	 2-(5-cloro-2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida	^{1}H NMR (HCl sal, CD_3OD, 400 MHz) 8.14 (s, 1H), 8.09 (m, 1H), 7.86 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.59 (m, 1H), 7.44 (m, 1H), 7.24 (s, 1H), 6.83 (s, 1H), 4.59 (m, 1H), 3.51 (m, 2H), 3.13 (m, 2H), 3.02 (m, 1H), 2.82 (s, 3H), 2.62 (s, 6H), 2.09 (s, 3H), 1.92 (m, 4H), 1.19 (d, *J* = 6.0 Hz, 6H). MS (ES^+): 573.1 $(M+1)^+$.
77	 5-cloro-N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(pirrolidin-1-ilsulfonil)fenil)pirimidina-2,4-diamina	^{1}H NMR (HCl sal, CD_3OD, 400 MHz) 8.14 (s, 1H), 8.09 (m, 1H), 7.89 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.58 (m, 1H), 7.40 (m, 1H), 7.28 (s, 1H), 6.83 (s, 1H), 4.59 (m, 1H), 3.51 (m, 2H), 3.13 (m, 6H), 3.02 (m, 1H), 2.82 (s, 3H), 2.09 (s, 3H), 1.91 (m, 4H), 1.67 (m, 4H), 1.20 (d, *J* = 6.0 Hz, 6H). MS (ES^+): 573.1 $(M+1)^+$.MS (ES^+): 599.3 $(M+1)^+$.
78	 5-cloro-N4-(2-(ciclobutilaminosulfonil)fenil)-N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)pirimidina-2,4-diamina	^{1}H NMR (HCl sal, CD_3OD, 400 MHz) 8.17 (s, 1H), 8.05 (m, 1H), 7.89 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.56 (m, 1H), 7.38 (m, 1H), 7.28 (s, 1H), 6.84 (s, 1H), 4.61 (m, 1H), 3.59 (m, 1H), 3.51 (m, 2H), 3.14 (m, 2H), 3.00 (m, 1H), 2.82 (s, 3H), 2.07 (s, 3H), 1.91 (m, 6H), 1.67 (m, 2H), 1.36 (m, 2H), 1.20 (d, *J* = 6.0 Hz, 6H). MS (ES^+):

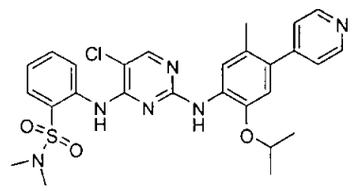
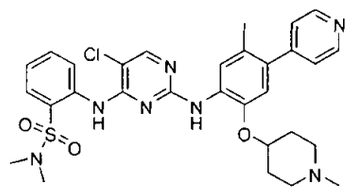
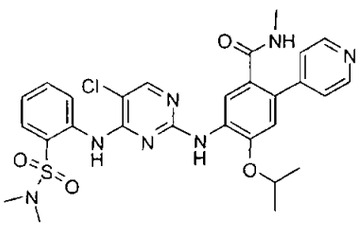
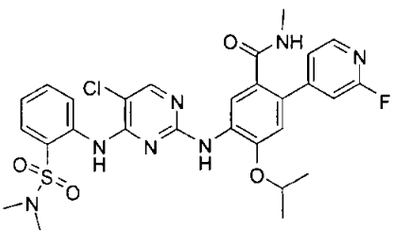
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
		599.3 $(M+1)^+$.
79	 2-(2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino)-5-cloropirimidin-4-ilamino)-N,N-dimetilbenzamida	^{1}H NMR (HCl sal, CD_3OD, 400 MHz) 8.15 (s, 1H), 7.78 (m, 1H), 7.59 (m, 1H), 7.54 (m, 1H), 7.46 (m, 1H), 7.33 (s, 1H), 6.90 (s, 1H), 4.69 (m, 1H), 3.61 (m, 2H), 3.22 (m, 2H), 3.09 (m, 1H), 3.06 (s, 3H), 2.92 (s, 6H), 2.17 (s, 3H), 2.00 (m, 4H), 1.30 (d, J = 6.0 Hz, 6H). MS (ES^+): 537.3 $(M+1)^+$.
80	 2-(2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino)-5-cloropirimidin-4-ilamino) benzamida	^{1}H NMR (HCl sal, CD_3OD, 400 MHz) 8.60 (s, 1H), 8.15 (s, 1H), 7.88 (m, 1H), 7.48 (m, 1H), 7.44 (m, 1H), 7.33 (m, 1H), 6.99 (s, 1H), 4.69 (m, 1H), 3.64 (m, 2H), 3.28 (m, 3H), 2.95 (s, 3H), 2.32 (s, 3H), 2.08 (m, 4H), 1.30 (d, J = 6.0 Hz, 6H). MS (ES^+): 509.2 $(M+1)^+$.
81	 5-cloro-N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(aminosulfonil)fenil)pirimidina-2,4-diamina	^{1}H NMR (HCl sal, CD_3OD, 400 MHz) 8.12 (s, 1H), 8.09 (s, 1H), 7.94 (dd, J = 8.0, 1.6 Hz, 1H), 7.52 (m, 1H), 7.36 (m, 1H), 7.28 (s, 1H), 6.85 (s, 1H), 4.60 (m, 1H), 3.51 (m, 2H), 3.09 (m, 2H), 3.02 (m, 1H), 2.82 (s, 3H), 2.11 (s, 3H), 1.92 (m, 4H), 1.19 (d, J = 6.0 Hz, 6H).MS (ES^+): 545.2 $(M+1)^+$.
82		^{1}H NMR (HCl sal, CD_3OD, 400 MHz) 8.14 (s, 1H), 8.04 (s, 1H), 8.00 (dd, J = 8.0, 1.6 Hz, 1H), 7.67 (m, 1H), 7.49 (m, 1H), 7.23 (s, 1H), 6.82 (s, 1H), 4.58 (m, 1H), 3.54 (m, 2H), 3.14 (m, 2H),

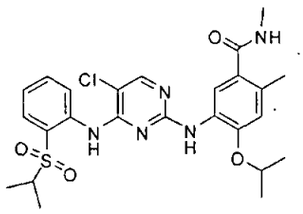
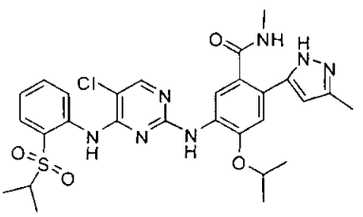
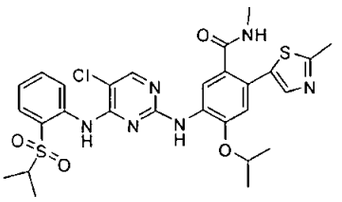
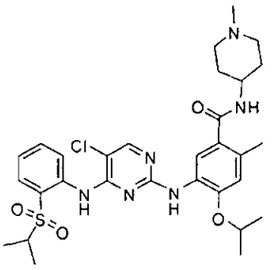
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
	5-cloro-N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(metilsulfonil)fenil)pirimidina-2,4-diamina	3.10 (s, 3H), 3.00 (m, 1H), 2.82 (s, 3H), 2.08 (s, 3H), 1.89 (m, 4H), 1.19 (d, J = 6.0 Hz, 6H). MS (ES^+): 544.2 $(M+1)^+$.
83	 5-cloro-N2-(2-fluoro-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(aminosulfonil)fenil)pirimidina-2,4-diamina	^{1}H NMR (HCl sal, DMSO-d6, 400 MHz) 9.61 (s, 1H), 9.39 (s, 1H), 9.11 (s, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.23 (s, 1H), 7.84 (dd, J = 8.0, 1.6 Hz, 1H), 7.70 (s, 2H), 7.41 (m, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.20 (m, 1H), 7.00 (d, J = 12.4 Hz, 1H), 3.52 (m, 2H), 3.11 (m, 2H), 2.99 (m, 1H), 2.82 (d, J = 4.8 Hz, 3H), 2.25 (s, 3H), 1.92 (m, 2H), 1.81(m, 2H). MS (ES^+): 505.2 $(M+1)^+$.
84	 5-cloro-N4-(2-(ciclobutilsulfonil)fenil)-N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)pirimidina-2,4-diamina	^{1}H NMR (HCl sal, CD_3OD, 400 MHz) 8.15 (s, 1H), 8.07 (s, 1H), 7.92 (dd, J = 8.0, 1.6 Hz, 1H), 7.65 (m, 1H), 7.47 (m, 1H), 7.20 (s, 1H), 6.84 (s, 1H), 4.58 (m, 1H), 3.99 (m, 1H), 3.52 (m, 2H), 3.14 (m, 2H), 3.02 (m, 1H), 2.83 (s, 3H), 2.35 (m, 2H), 2.08 (s, 3H), 2.00 (m, 2H),1.89 (m, 6H), 1.19 (d, J = 6.0 Hz, 6H). MS (ES^+): 584.2 $(M+1)^+$.
85	 5-cloro-N4-(2-(isopropilsulfonil)fenil)-N2-(2-metoxi-5-metil-4-fenil)-fenil)pirimidina-2,4-diamina	MS (ES^+): 523.2 $(M+1)^+$.

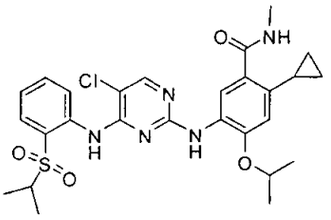
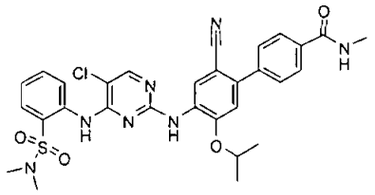
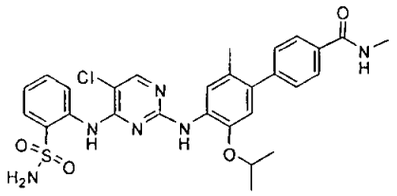
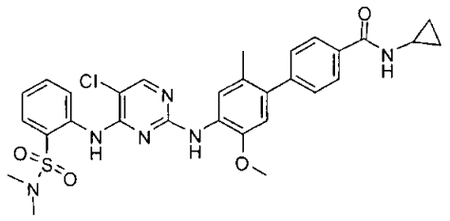
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
86	 5-cloro-N4-(2-cianofenil)-N2-(2-metoxi-5-metil-4-fenil)-fenil)pirimidina-2,4-diamina	MS (ES^+): 442.1 $(M+1)^+$.
87	 2-(5-cloro-2-(5-metoxi-2-metilbifenil-4-ilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida	MS (ES^+): 524.1 $(M+1)^+$.
88	 5-cloro-N4-(2-(isopropilsulfonil)fenil)-N2-(2-metoxi-5-metil-4-(4-metilfenil)-fenil)pirimidina-2,4-diamina	MS (ES^+): 537.0 $(M+1)^+$.
89	 5-cloro-N4-(2-(isopropilsulfonil)fenil)-N2-(2-metoxi-5-metil-4-(4-fluorofenil)-fenil)pirimidina-2,4-diamina	MS (ES^+): 541.1 $(M+1)^+$.
90	 5-cloro-N4-(2-(isopropilsulfonil)fenil)-N2-(2-metoxi-5-metil-4-(2,4-difluorofenil)-fenil)pirimidina-2,4-diamina	MS (ES^+): 559.0 $(M+1)^+$.

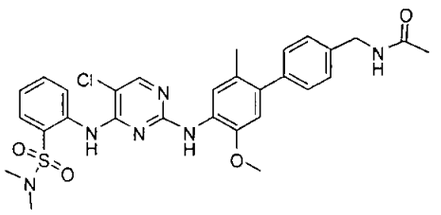
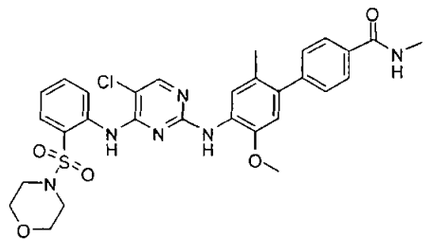
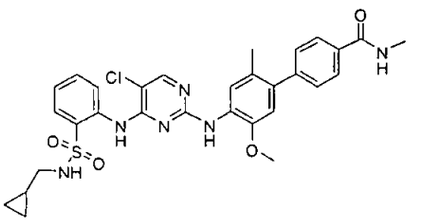
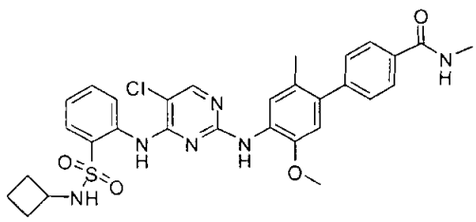
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
91	 2-(5-cloro-2-(4'-(dimetilamino)-5-metoxi-2,3'-dimetilbifenil-4-ilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida	MS (ES^+): 581.2 $(M+1)^+$.
92	 5-cloro-N2-(2-isopropoxi-5-metil-4-((1s,4s)-4-(pirrolidin-1-il)ciclohexil)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES^+): 626.3 $(M+1)^+$.
93	 2-(5-cloro-2-(5-metoxi-2-metil-4'-morfolinobifenil-4-ilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida	MS (ES^+): 609.2 $(M+1)^+$.
94	 2-(5-cloro-2-(5-metoxi-2-metil-4'-(metilsulfonil)bifenil-4-ilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida	MS (ES^+): 602.1 $(M+1)^+$.
95		MS (ES^+): 567.2 $(M+1)^+$.

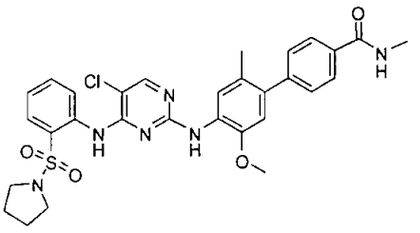
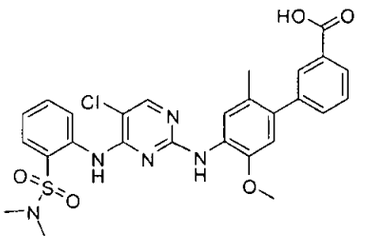
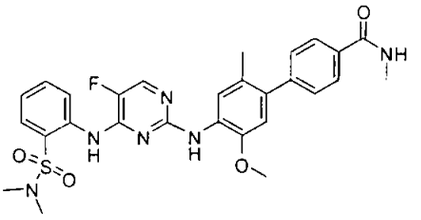
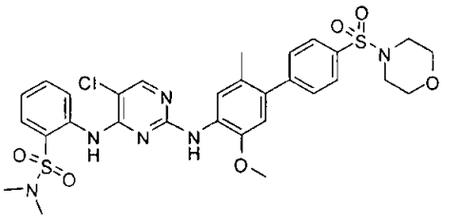
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
	4'-(5-cloro-4-(2-(N,N-dimetilsulfamoil) fenilamino)pirimidin-2-ilamino)-5'-metoxi-2'-metilbifenil-4-carboxamida	
96	 2-(2-(4'-acetil-5-metoxi-2-metilbifenil-4-ilamino)-5-cloropirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida	MS (ES^+): 566.2 $(M+1)^+$.
97	 4'-(5-cloro-4-(2-(N,N-dimetilsulfamoil) fenilamino)pirimidin-2-ilamino)-5'-metoxi-N,2'-dimetilbifenil-4-carboxamida	MS (ES^+): 581.2 $(M+1)^+$.
98	 ácido 4'-(5-cloro-4-(2-(N,N-dimetilsulfamoil) fenilamino)pirimidin-2-ilamino)-5'-metoxi-2'-metilbifenil-4-carboxílico	MS (ES^+): 568.1 $(M+1)^+$.
99	 2-(5-cloro-2-(2-metoxi-5-metil-4-(piridin-4-il)fenilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida	MS (ES^+): 525.1 $(M+1)^+$.

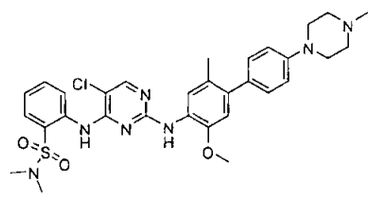
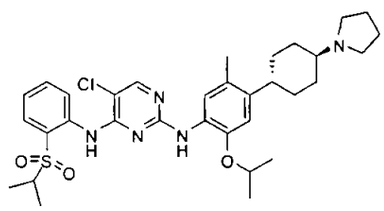
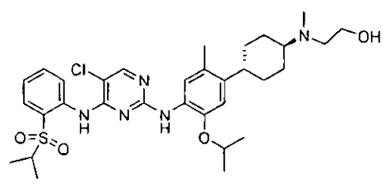
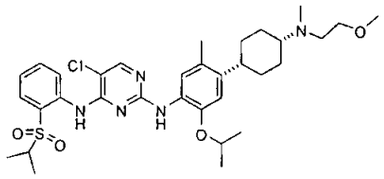
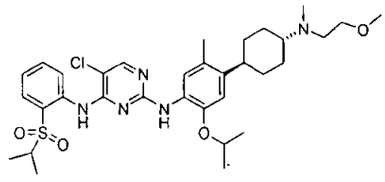
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
100	 2-(5-cloro-2-(2-isopropoxi-5-metil-4-(piridin-4-il)fenilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida	MS (ES^+): 553.2 $(M+1)^+$.
101	 2-(5-cloro-2-(5-metil-2-(1-metilpiperidin-4-iloxi)-4-(piridin-4-il)fenilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida	MS (ES^+): 608.2 $(M+1)^+$.
102	 5-(5-cloro-4-(2-(N,N-dimetilsulfamoil) fenilamino)pirimidin-2-ilamino)-4-isopropoxi-N-metil-2-(piridin-4-il)benzamida	MS (ES^+): 596.2 $(M+1)^+$.
103	 5-(5-cloro-4-(2-(N,N-dimetilsulfamoil) fenilamino)pirimidin-2-ilamino)-2-(2-fluoropiridin-4-il)-4-isopropoxi-N-metilbenzamida	MS (ES^+): 614.2 $(M+1)^+$.

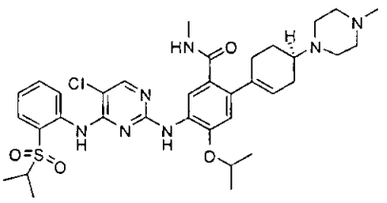
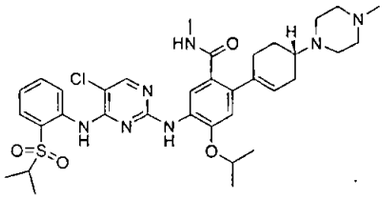
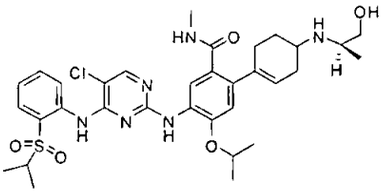
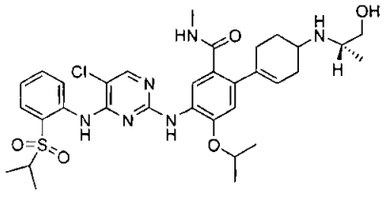
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
104	 5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N,2-dimetilbenzamida	MS (ES^+): 532.0 $(M+1)^+$.
105	 5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metil-2-(3-metil-1H-pirazol-5-il)benzamida	MS (ES^+): 598.2 $(M+1)^+$.
106	 5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metil-2-(2-metiltiazol-5-il)benzamida	MS (ES^+): 615.2 $(M+1)^+$.
107	 5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-2-metil-N-(1-metilpiperidin-4-il)benzamida	MS (ES^+): 615.2 $(M+1)^+$.

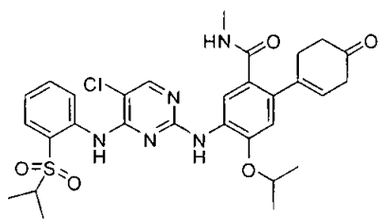
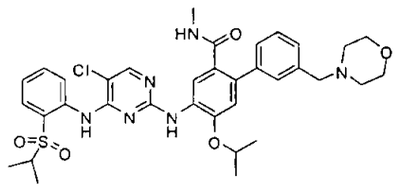
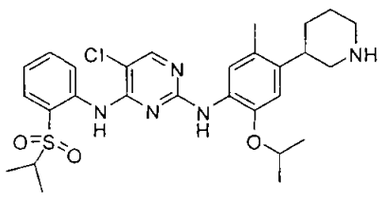
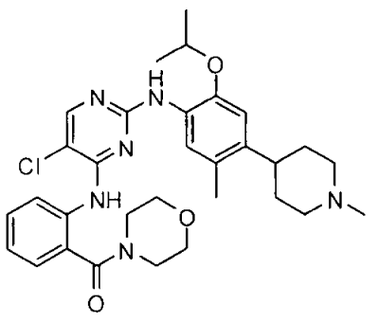
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
108	 5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2-ciclopropil-4-isopropoxi-N-metilbenzamida	MS (ES^+): 558.2 $(M+1)^+$.
109	 4'-(5-cloro-4-(2-(N,N-dimetilsulfamoil) fenilamino)pirimidin-2-ilamino)-2'-ciano-5'-isopropoxi-N-metilbifenil-4-carboxamida	MS (ES^+): 620.2 $(M+1)^+$.
110	 5-cloro-N4-(2-(sulfonilamino)fenil)-N2-(2-metoxi-5-metil-4-(3-metil-4-(metilacetamidofenil)-fenil)pirimidina-2,4-diamina	MS (ES^+): 581.2 $(M+1)^+$.
111	 4'-(5-cloro-4-(2-(N,N-dimetilsulfamoil) fenilamino)pirimidin-2-ilamino)-N-ciclopropil-5'-metoxi-2'-metilbifenil-4-carboxamida	MS (ES^+): 607.2 $(M+1)^+$.

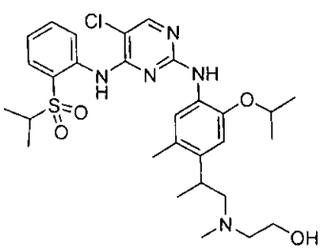
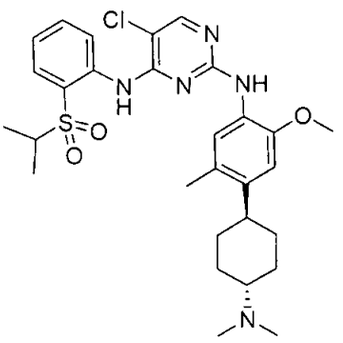
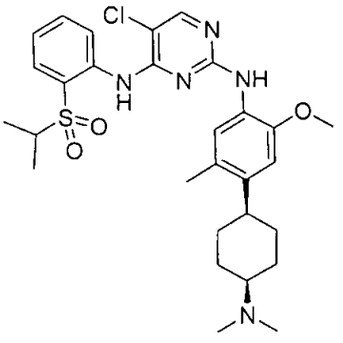
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
112	 N-((4'-(5-cloro-4-(2-(N,N-dimetilsulfamoil) fenilamino)pirimidin-2-ilamino)-5'-metoxi-2'-metilbifenil-4-il)metil)acetamida	MS (ES^+): 595.2 $(M+1)^+$.
113	 5-cloro-N4-(2-(morfolinosulfonil)fenil)-N2-(2-metoxi-5-metil-4-(4-(metilacetamidofenil)-fenil)pirimidina-2,4-diamina	MS (ES^+): 623.2 $(M+1)^+$.
114	 4'-(5-cloro-4-(2-(N-(ciclopropilmetil) sulfamoil)fenilamino)pirimidin-2-ilamino)-5'-metoxi-N,2'-dimetilbifenil-4-carboxamida	MS (ES^+): 607.1 $(M+1)^+$.
115	 4'-(5-cloro-4-(2-(N-ciclobutilsulfamoil) feniłamino)pirimidin-2-ilamino)-5'-metoxi-N,2'-dimetilbifenil-4-carboxamida	MS (ES^+): 607.1 $(M+1)^+$.

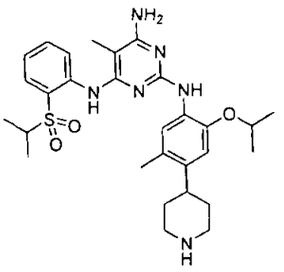
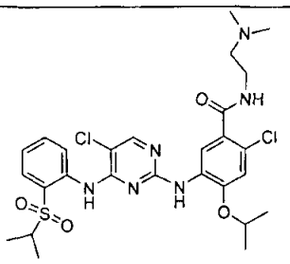
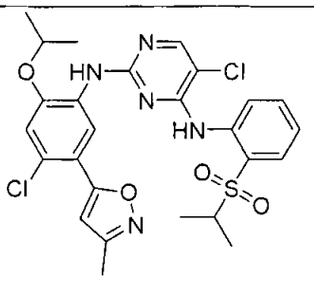
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
116	 5-cloro-N4-(2-(pirrolidinosulfonil)fenil)-N2-(2-metoxi-5-metil-4-(4-acetamidometilfenil)-fenil)pirimidina-2,4-diamina	MS (ES^+): 607.2 $(M+1)^+$.
117	 ácido 4'-(5-cloro-4-(2-(N,N-dimetilsulfamoil) fenilamino)pirimidin-2-ilamino)-5'-metoxi-2'-metilbifenil-3-carboxílico	MS (ES^+): 568.1 $(M+1)^+$.
118	 4'-(4-(2-(N,N-dimetilsulfamoil)fenilamino)-5-fluoropirimidin-2-ilamino)-5'-metoxi-N,2'-dimetilbifenil-4-carboxamida	MS (ES^+): 565.2 $(M+1)^+$.
119	 2-(5-cloro-2-(5-metoxi-2-metil-4'-(morfolinosulfonil)bifenil-4-ilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida	MS (ES^+): 673.2 $(M+1)^+$.

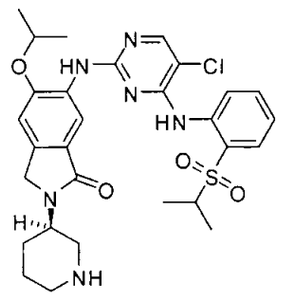
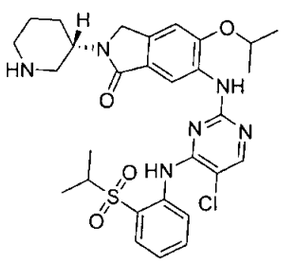
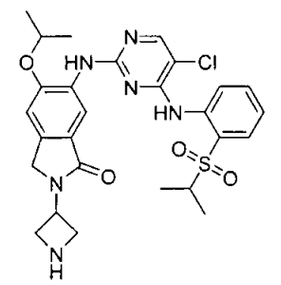
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
120	 2-(5-cloro-2-(5-metoxi-2-metil-4'-(4-metilpiperazin-1-il)bifenil-4-ilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida	MS (ES^+): 622.2 $(M+1)^+$.
121	 5-cloro-N2-(2-isopropoxi-5-metil-4-((1r,4r)-4-(pirrolidin-1-il)ciclohexil)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES^+): 626.3 $(M+1)^+$.
122	 2-(N-((1r,4r)-4-(4-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-metilfenil)ciclohexil)-N-metilamino)etanol	MS (ES^+): 630.3 $(M+1)^+$.
123	 N2-(4-((1s,4s)-4-(N-(2-metoxietil)-N-metilamino)ciclohexil)-2-isopropoxi-5-metilfenil)-5-cloro-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina	MS (ES^+): 644.3 $(M+1)^+$.
124	 N2-(4-((1r,4r)-4-(N-(2-metoxietil)-N-metilamino)ciclohexil)-2-isopropoxi-5-metilfenil)-5-cloro-N4-(2-	MS (ES^+): 644.3 $(M+1)^+$.

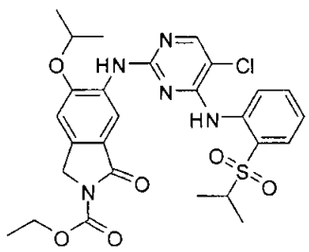
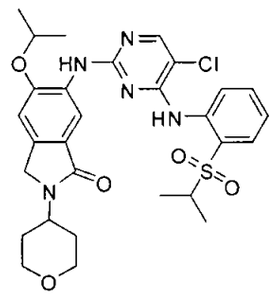
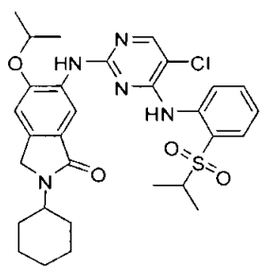
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
	(isopropilsulfonil)fenil)pirimidina-2,4-diamina	
125	 5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metil-2-((R)-4-(4-metilpiperazin-1-il)ciclohex-1-enil)benzamida	MS (ES^+): 696.3 $(M+1)^+$.
126	 5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metil-2-((S)-4-(4-metilpiperazin-1-il)ciclohex-1-enil)benzamida	MS (ES^+): 696.3 $(M+1)^+$.
127	 2-(4-((R)-1-hidroxipropan-2-ilamino)ciclohex-1-enil)-5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metilbenzamida	MS (ES^+): 671.3 $(M+1)^+$.
128	 2-(4-((S)-1-hidroxipropan-2-ilamino)ciclohex-1-enil)-5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metilbenzamida	MS (ES^-): 671.3 $(M+1)^+$.

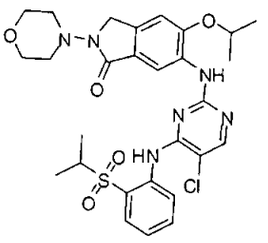
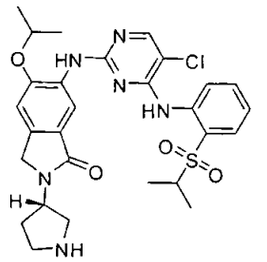
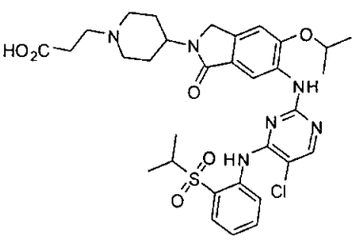
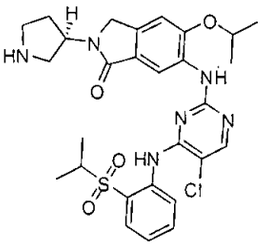
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
129	 5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metil-2-(4-oxociclohex-1-enil)benzamida	MS (ES^+): 612.2 $(M+1)^+$.
130	 5-cloro-N4-(2-(isopropilsulfony)fenil)-N2-(2-isopropoxi-5-(N-metilcarboxamido)-4-(3-metil-4-(3-morfolinometil)-fenil)pirimidina-2,4-diamina	MS (ES^+): 693.3 $(M+1)^+$.
131	 5-cloro-N2-(2-isopropoxi-5-metil-4-(piperidin-3-il)fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina	MS (ES^+): 558.2 $(M+1)^+$.
132	 (2-(5-cloro-2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino)pirimidin-4-ilamino)fenil)(morfolino)metanona	MS (ES^+): 579.1 $(M+1)^+$.

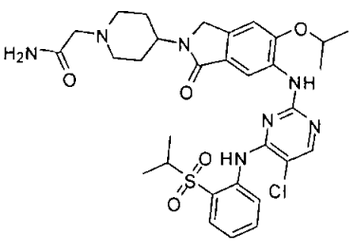
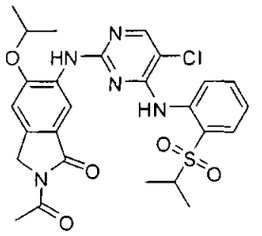
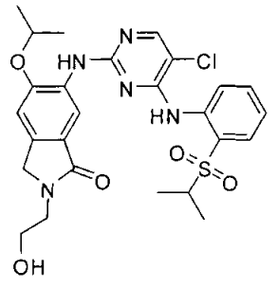
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
133	 2-((2-(4-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) pirimidin-2-ilamino)-5-isopropoxi-2-metilfenil) propil)(metil)amino)etanol	MS (ES^+): 590.1 $(M+1)^+$.
134	 5-cloro-N2-(4-((1r,4r)-4-(dimetilamino) ciclohexil)-2-metoxi-5-metilfenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina	MS (ES^+): 572.1 $(M+1)^+$.
135	 5-cloro-N2-(4-((1s,4s)-4-(dimetilamino) ciclohexil)-2-metoxi-5-metilfenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina	MS (ES^+): 572.1 $(M+1)^+$.

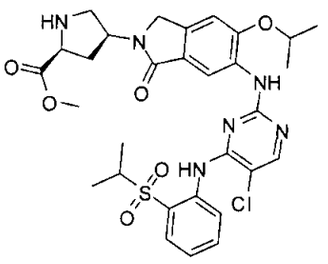
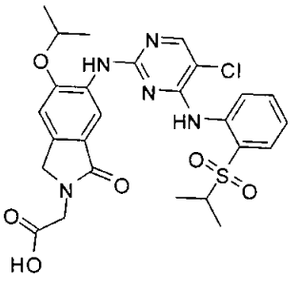
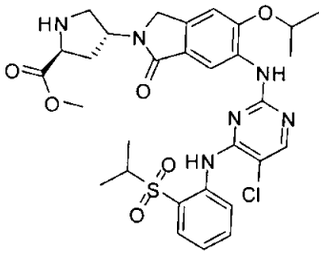
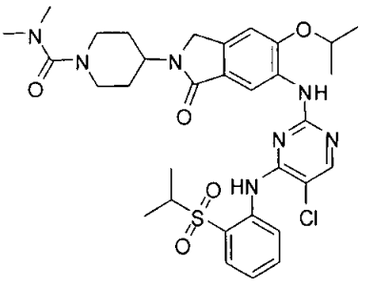
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
136	 N2-(2-isopropoxi-5-metil-4-(piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-5-metilpirimidina-2,4,6-triamina	MS (ES^+): 552.7 $(M+1)^+$.
137	 5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2-cloro-N-(2-(dimetilamino)etil)-4-isopropoxibenzamida	MS (ES^+): 610.0 $(M+1)^+$.
138	 5-cloro-N2-(4-cloro-2-isopropoxi-5-(3-metilisoxazol-5-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES^+): 577.5 $(M+1)^+$.

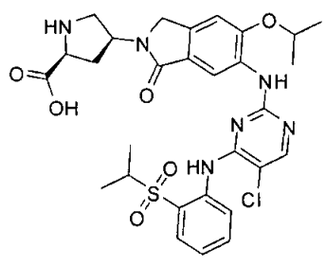
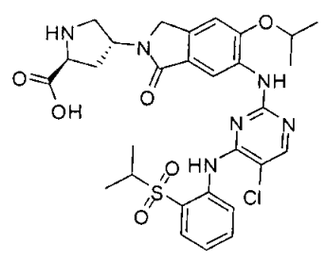
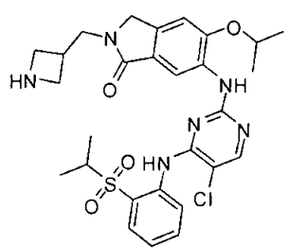
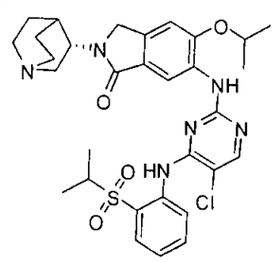
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
139	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-((R)-piperidin-3-il)isoindolin-1-ona	MS (ES^+): 599.2 $(M+1)^+$.
140	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-((S)-piperidin-3-il)isoindolin-1-ona	MS (ES^+): 599.2 $(M+1)^+$.
141	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2-(azetidin-3-il)-5-isopropoxiisoindolin-1-ona	MS (ES^+): 571.2 $(M+1)^+$.

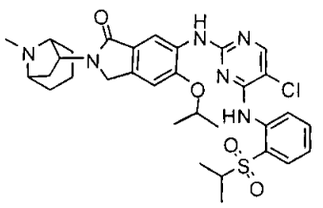
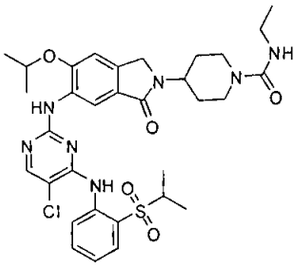
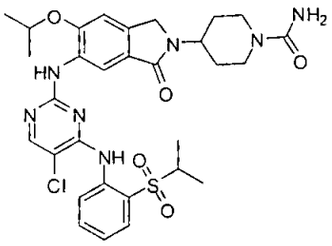
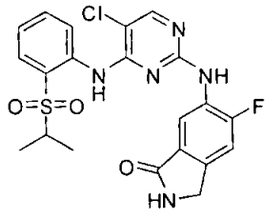
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
142	 Etil 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindoline-2-carboxilato	MS (ES^+): 588.2 $(M+1)^+$.
143	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2-(tetrahidro-2H-piran-4-il)-5-isopropoxiisoindolin-1-ona	MS (ES^+): 600.2 $(M+1)^+$.
144	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloro pirimidin-2-ilamino)-2-ciclohexil-5-isopropoxi-isoindolin-1-ona	MS (ES^+): 598.2 $(M+1)^+$.

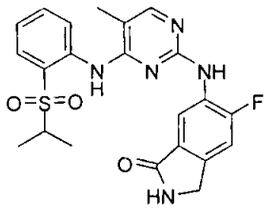
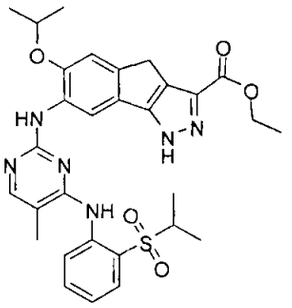
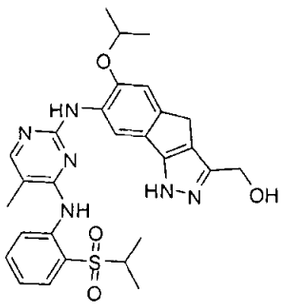
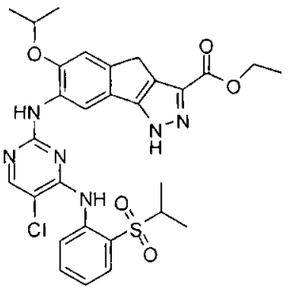
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
145	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloro pirimidin-2-ilamino)-5-isopropoxi-2-morfolino-isoindolin-1-ona	MS (ES^+): 601.2 $(M+1)^+$.
146	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-((S)-pirrolidin-3-il)isoindolin-1-ona	MS (ES^+): 585.2 $(M+1)^+$.
147	 ácido 3-(4-(6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)piperidin-1-il)propanoico	MS (ES^+): 671.2 $(M+1)^+$.
148	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-((R)-pirrolidin-3-il)isoindolin-1-ona	MS (ES^+): 585.2 $(M+1)^+$.

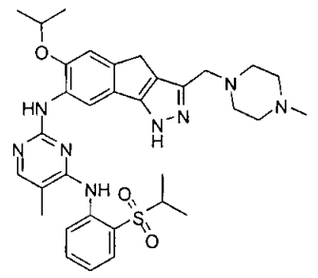
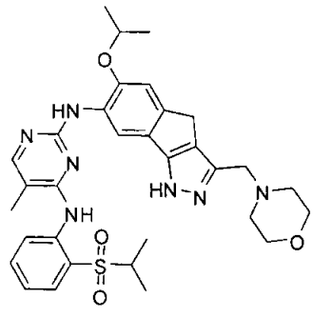
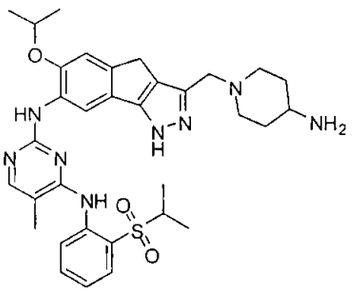
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
149	 2-[4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenil-amino]-pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro-isoindol-2-il)-piperidin-1-il]-acetamida	MS (ES^+): 656.2 $(M+1)^+$.
150	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2-acetil-5-isopropoxiisoindolin-1-ona	MS (ES^+): 558.2 $(M+1)^+$.
151	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2-(2-hidroxietil)-5-isopropoxiisoindolin-1-ona	MS (ES^+): 560.2$(M+1)^+$.

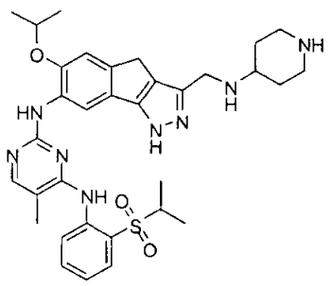
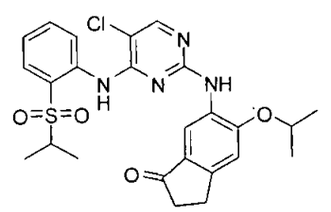
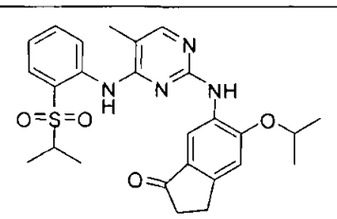
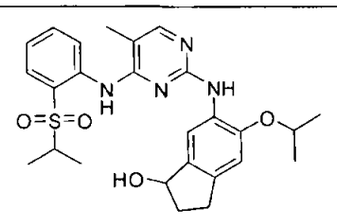
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
152	 (2S,4S)-metil 4-(6-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)pirrolidina-2-carboxilato	MS (ES^+): 643.2 $(M+1)^+$.
153	 ácido 2-(6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)acético	MS (ES^+): 574.1 $(M+1)^+$.
154	 (2S,4R)-metil 4-(6-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)pirrolidina-2-carboxilato	MS (ES^+): 643.2 $(M+1)^+$.
155	 dimetilamida del ácido 4-(6-{5-Cloro-4-[2-(propano-2-	^{1}H NMR (400 MHz, MeOD-d_4) δ 8.29 (s, 1H), 8.26 (br, 1H), 7.96 (dd, 1H), 7.93 (s, 1H), 7.72(dd, 1H), 7.48 (dd, 1H), 7.35 (s, 1H), 4.50 (s, 2H), 4.35-4.29 (m, 1H), 3.83 (d, 2H), 3.38-3.30 (m, 2H), 3.02-2.95 (m, 3H), 2.88 (s, 6H), 1.88-1.84 (m, 3H), 1.36 (d,

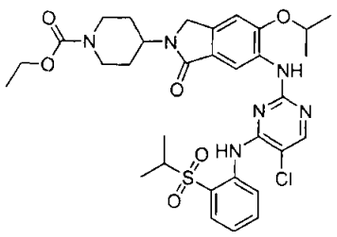
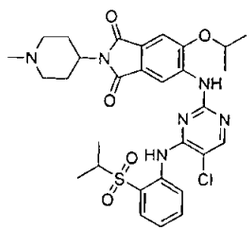
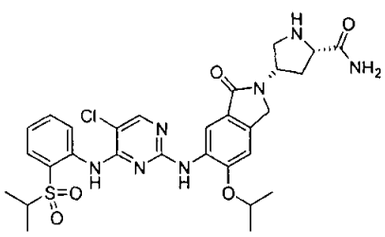
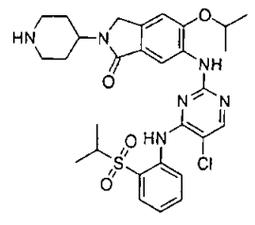
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
	sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro-isoindol-2-il)-piperidina-1-carboxílico	6H), 1.25 (d, 6H); ESMS *m/z* 670.2 (M + H$^+$).
156	 ácido (2S,4S)-4-(6-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)pirrolidina-2-carboxílico	MS (ES$^+$): 629.2 (M+1)$^+$.
157	 ácido (2S,4R)-4-(6-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)pirrolidina-2-carboxílico	MS (ES$^+$): 629.2 (M+1)$^+$.
158	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2-((azetidin-3-il)metil)-5-isopropoxiisoindolin-1-ona	MS (ES$^+$): 585.2 (M+1)$^+$.
159	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-	MS (ES$^+$): 625.2 (M+1)$^+$.

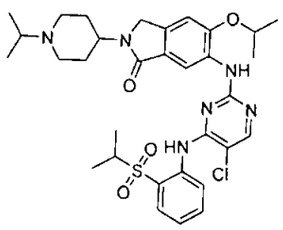
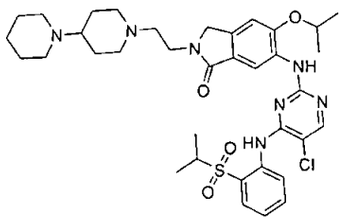
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
	ilamino)-5-isopropoxi-2-((S)-quinuclidin-3-il)isoindolin-1-ona	
160	 6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-(8-metil-8-aza-biciclo[3.2.1]oct-6-il)-2,3-dihidro-isoindol-1-ona	MS (ES^+): 639.2 $(M+1)^+$.
161	 4-(6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)-N-etilpiperidina-1-carboxamida	MS (ES^+): 670.3 $(M+1)^+$.
162	 4-(6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)piperidina-1-carboxamida	MS (ES^+): 642.1 $(M+1)^+$.
163	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-fluoroisoindolin-1-ona	MS (ES^+): 476.1 $(M+1)^+$.

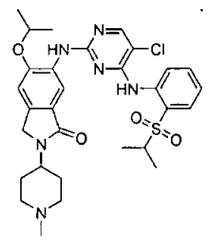
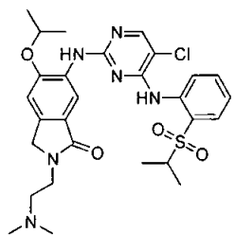
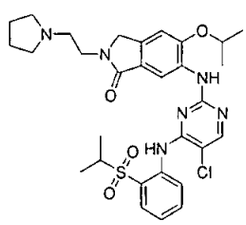
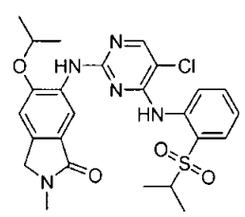
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
164	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-metilpirimidin-2-ilamino)-5-fluoroisoindolin-1-ona	MS (ES^+): 456.1 $(M+1)^+$.
165	 Etil 7-(4-(2-(isopropilsulfonil)fenilamino)-5-metilpirimidin-2-ilamino)-1,4-dihidro-6-isopropoxiindeno[1,2-c]pirazol-3-carboxilato	MS (ES^+): 591.2 $(M+1)^+$.
166	 (7-(4-(2-(isopropilsulfonil)fenilamino)-5-metilpirimidin-2-ilamino)-1,4-dihidro-6-isopropoxiindeno[1,2-c]pirazol-3-il)metanol	MS (ES^+): 549.2 $(M+1)^+$.
167	 Etil 7-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-	MS (ES^+): 611.2 $(M+1)^+$.

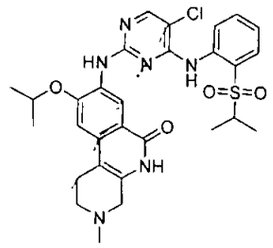
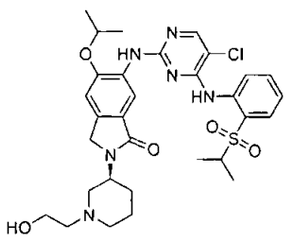
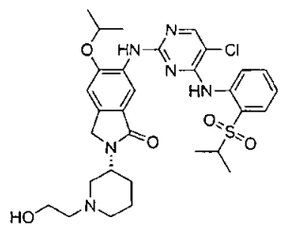
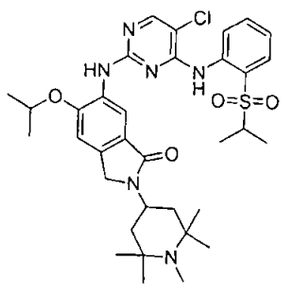
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
	ilamino)-1,4-dihidro-6-isopropoxiindeno[1,2-c]pirazol-3-carboxilato	
168	 N2-(1,4-dihidro-6-isopropoxi-3-((4-metilpiperazin-1-il)metil)indeno[1,2-c]pirazol-7-il)-N4-(2-(isopropilsulfonil)fenil)-5-metilpirimidina-2,4-diamina	MS (ES^+): 631.3 $(M+1)^+$.
169	 N2-(1,4-dihidro-6-isopropoxi-3-(morfolinometil) indeno[1,2-c]pirazol-7-il)-N4-(2-(isopropilsulfonil) fenil)-5-metilpirimidina-2,4-diamina	MS (ES^+): 618.3 $(M+1)^+$.
170	 N2-(3-((4-aminopiperidin-1-il)metil)-1,4-dihidro-6-isopropoxiindeno[1,2-c]pirazol-7-il)-N4-(2-(isopropilsulfonil)fenil)-5-metilpirimidina-2,4-diamina	MS (ES^+): 631.3 $(M+1)^+$.

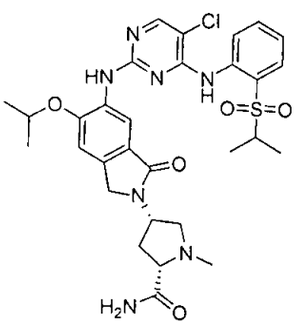
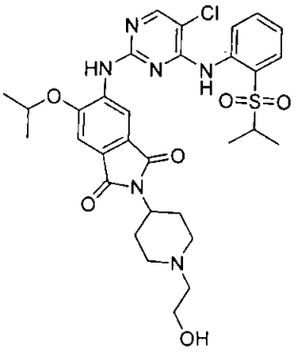
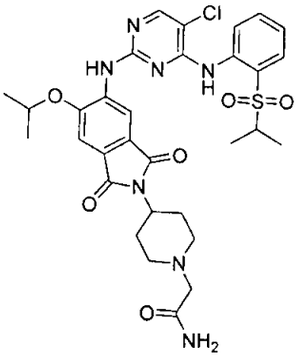
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
171	 N2-(1,4-dihidro-6-isopropoxi-3-((piperidin-4-ilamino)metil)indeno[1,2-c]pirazol-7-il)-N4-(2-(isopropilsulfonil)fenil)-5-metilpirimidina-2,4-diamina	MS (ES^+): 631.3 $(M+1)^+$.
172	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2,3-dihidro-5-isopropoxiinden-1-ona	MS (ES^+): 515.1 $(M+1)^+$.
173	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-metilpirimidin-2-ilamino)-2,3-dihidro-5-isopropoxiinden-1-ona	MS (ES^+): 495.2 $(M+1)^+$.
174	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-metil pirimidin-2-ilamino)-2,3-dihidro-5-isopropoxi-1H-inden-1-ol	MS (ES^+): 497.2 $(M+1)^+$.

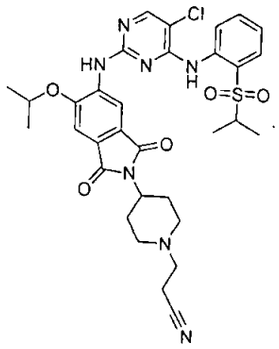
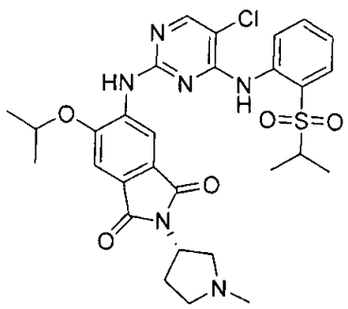
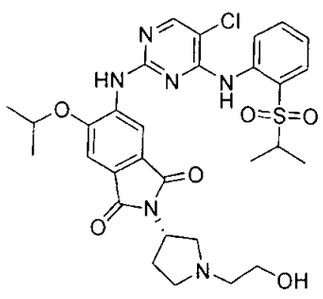
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
175	 éster etílico del ácido 4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino] -pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro -isoindol-2-il)-piperidina-1-carboxílico	^{1}H NMR 400 MHz (DMSO-d_6 con trazas D_2O) δ 8.55 (d, 1H), 8.32 (s, 1H), 8.14 (s, 1H), 7.82 (dd,1H), 7.74 (t, 1H), 7.34 (t, 1H), 7.28 (s, 1H), 4.73 (m, 2H), 4.39 (s, 2H), 4.12 (m, 2H), 4.06 (q, 2H), 3.46 (m, 1H), 2.92 (m 2H), 1.76 (m, 2H), 1.68 (m, 2H), 1.29 (d, 6H), 1.20 (t, 3H), 1.17 (d, 6H); MS m/z 671 (M+1).
176	 5-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-6-isopropoxi-2-(1-metil-piperidin-4-il)-isoindol-1,3-diona	^{1}H NMR 400 MHz (DMSO-d_6 con trazas D_2O) δ 8.44 (s, 2H), 8.39 (s, 1H), 7.87 (dd, 1H), 7.78 (dt, 1H), 7.45 (s, 1H), 7.41 (m, 1H), 4.91(m, 2H), 4.25(m, 2H), 3.51 (m, 3H), 3.10(m, 2H), 2.77(s, 3H), 1.80(m, 2H), 1.35(d, 6H), 1.13(d, 6H); MS m/z 627 (M+1).
177	 amida del ácido (2S, 4S)-4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro-isoindol-2-il)-pirrolidina-2-carboxílico	^{1}H NMR 400 MHz (DMSO-d_6 con trazas D_2O) δ 8.47(d, 1H), 8.25 (s, 1H), 8.07 (s, 1H), 7.78 (dd, 1H), 7.68 (m, 1H), 7.31(t, 1H), 7,24 (s, 1H), 4,71 (m, 2H), 4.43 (dd, 2H), 3.60 (m, 1H), 3.44 (m, 1H), 3.35 (m,1H), 2.63 (m, 1H), 2.28 (m, 1H), 1.22 (d, 6H), 1.10 (d, 6H); MS m/z 628 (M+1).
178		^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 10.13 (s, 1H), 9.60-9.50 (br, 1H), 9.34-9.21 (br, 1H), 8.46 (d, 1H), 8.26 (s, 1H), 8.08 (s, 1H), 7.91 (dd, 1H), 7.71 (m, 1H), 7.34 (t, 1H), 7.03 (s, 1H),

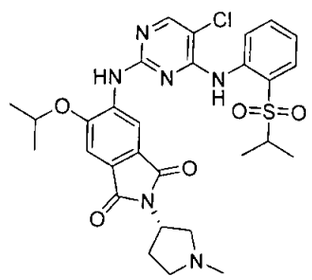
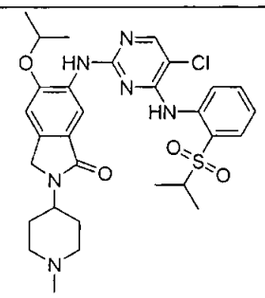
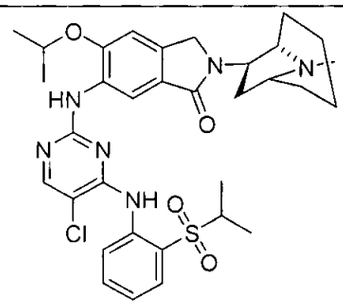
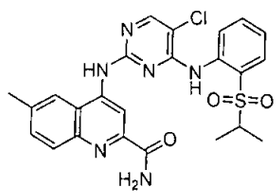
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
	6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-piperidin-4-il-2,3-dihidro-isoindol-1-ona	4.30 (m, 1H), 4.53 (m, 1H), 4.33 (s, 2H), 3.62 (m, 2H), 3.21-3.09 (m, 3H), 2.31-2.21 (m, 2H), 2.09-2.05 (m, 2H), 1.41 (d, 6H), 2.30 (d, 6H); ESMS *m/z* 599.2 ($M + H^+$).
179	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-(1-isopropilpiperidin-4-il)isoindolin-1-ona	MS (ES^+): 641.3 $(M+1)^+$.
180	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-(2-(4-(piperidin-1-il)piperidin-1-il)etil)isoindolin-1-ona	MS (ES^+): 710.3 $(M+1)^+$.

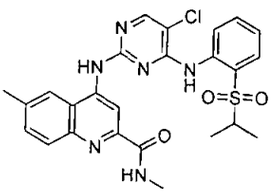
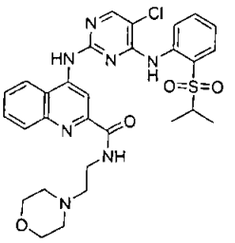
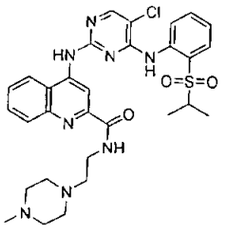
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
181	 6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-(1-metil-piperidin-4-il)-2,3-dihidro-isoindol-1-ona	^{1}H NMR 400 MHz (DMSO-d_6 con trazas D_2O) δ 8.46 (d, 1H), 8.35 (s, 1H), 8.09(s, 1H), 7.82(d, 1H), 7.74(t, 1H), 7.36(t,1H), 7.33(s, 1H), 4.75 (m, 1H), 4.41(s, 2H), 4,29(m, 1H), 3.65(m, 2H), 3.44(m, 1H), 3.17(t, 2H), 2,79(s, 3H), 2.07(m, 2H), 1,98(d, 2H), 1.28(d, 6H), 1.14(d, 6H); MS m/z 613 (M+1).
182	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloro pirimidin-2-ilamino)-2-(1-(2-(dimetilamino)etil) piperidin-4-il)-5-isopropoxiisoindolin-1-ona	8.60(d,1H), 8.33(s,1H);8.20 (s,1H);7.82(dd,1H);7.77(dt, 1H); 7.35(s, 1H); 7.33(t,1H); 4.76 (m, 1H); 4.44(s,2H); 3.88 (t, 2H); 3.40 (m, 3H); 2.87 (s, 6H); 1,30 (d, 6H); 1.16 (d, 6H).). MS (ES^+): 587.2 $(M+1)^+$.
183	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-(1-(2-(pirrolidin-1-il)etil)piperidin-4-il)isoindolin-1-ona	8.60(d,1H); 8.32(s,1H);8.20 (s, 1H);7.83(dd,1H);7.78 (dt,1H);7.35 (s,1H);7.31(t,1H);4.76(m, 1H);4.46(s,2H);3.87 (t,2H); 3.63 (m,2H); 3.48 (m,1H); 3.09 (m,2H); 2.05 (m, 2H); 1.85 (m, 2H); 1.30(d,6H); 1.17(d,6H). MS (ES^+): 613.2 $(M+1)^+$.
184	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-metilisoindolin-1-ona	8.53(d, 1H); 8.32(s, 1H), 8.11(s, 1H); 7.81(dd, 1H); 7.73(dt, 1H); 7.33(t, 1H);7.28(s, 1H);4.72 (m,1H); 4.39 (s, 2H); 3.30 (m, 1H); 3.06(s, 3H); 1.28 (d, 6H), 1.15 (d, 6H). MS (ES^+): 530.2 $(M+1)^+$.

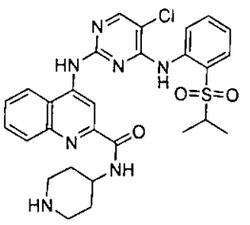
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
185	 8-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) pirimidin-2-ilamino)-9-isopropoxi-3-metil-1,2,3,4-tetrahidrobenzo[c][1,7]naftiridin-6(5H)-ona	MS (ES^+): 597.1 $(M+1)^+$.
186	 (S)-6-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) pirimidin-2-ilamino)-2-(1-(2-hidroxietil)piperidin-3-il)-5-isopropoxiisoindolin-1-ona	MS (ES^+): 643.2 $(M+1)^+$.
187	 (R)-6-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) pirimidin-2-ilamino)-2-(1-(2-hidroxietil)piperidin-3-il)-5-isopropoxiisoindolin-1-ona	MS (ES^+): 643.2 $(M+1)^+$.
188	 6-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) pirimidin-2-ilamino)-5-isopropoxi-2-(1,2,2,6,6-pentametilpiperidin-4-il)isoindolin-1-ona	MS (ES^+): 669.3 $(M+1)^+$.

	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
189	 (2S,4S)-4-(6-(5-cloro-4-(2-(isopropilsulfonil) fenilamino)pirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)-1-metilpirrolidina-2-carboxamida	MS (ES^+): 642.2 $(M+1)^+$.
190	 5-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) pirimidin-2-ilamino)-2-(1-(2-hidroxietil)piperidin-4-il)-6-isopropoxiisoindoline-1,3-diona	MS (ES^+): 657.2 $(M+1)^+$.
191	 2-(4-(5-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) pirimidin-2-ilamino)-6-isopropoxi-1,3-dioxoisoindolin-2-il)piperidin-1-il)acetamida	MS (ES^+): 670.2 $(M+1)^+$.

	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
192	 3-(4-(5-(5-cloro-4-(2-(isopropilsulfonil) fenilamino)pirimidin-2-ilamino)-6-isopropoxi-1,3-dioxoisoindolin-2-il)piperidin-1-il)propanonitrilo	MS (ES$^+$): 666 (M+1)$^+$.
193	 (S)-5-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) pirimidin-2-ilamino)-6-isopropoxi-2-(1-metilpirrolidin-3-il)isoindoline-1,3-diona	MS (ES$^+$): 613.1 (M+1)$^+$.
194	 (S)-5-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) pirimidin-2-ilamino)-2-(1-(2-hidroxietil)pirrolidin-3-il)-6-isopropoxiisoindoline-1,3-diona	MS (ES$^+$): 643.1 (M+1)$^+$.

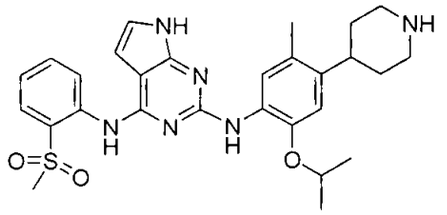
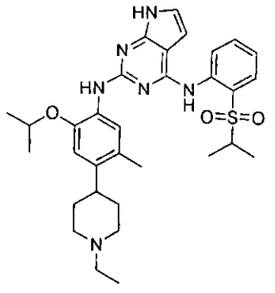
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
195	 (S)-5-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) pirimidin-2-ilamino)-6-isopropoxi-2-(1-metilpirrolidin-3-il)isoindoline-1,3-diona	MS (ES^+): 613.1 $(M+1)^+$.
196	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-(1-metilpiperidin-4-il)isoindolin-1-ona	8.44(s,2H);8.39(s,1H);7.87(dd,1H);7.78(dt,1H);7.45(s,1H);7.41(m,1H);4.91(m,2H); 4.25(m,2H); 3.51 (m,3H); 3.10 (m,2H); 2.77 (s,3H); 1.80(m,2H),1.35(d,6H);1.13(d,6H). MS (ES^+): 614.2 $(M+1)^+$.
197	 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-((6S,7R)-9-metil-9-aza-biciclo[4.2.1]nonan-7-il)isoindolin-1-ona	MS (ES^+): 654.2 $(M+1)^+$.
198	 amida del ácido 4-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-6-metil-quinolina-2-	^{1}H NMR (DMSO, 400 MHz) δ 10.04 (s, 1H), 9.66 (s, 1H), 8.47-8.63 (m, 3H), 8.18-8.23 (m, 2H), 7.97-7.99 (d, 1H), 7.54-7.82 (m, 3H), 7.25-7.35 (m, 1H), 3.31-3.33 (m, 1H), 2.54 (s, 3H),

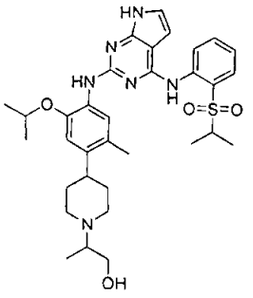
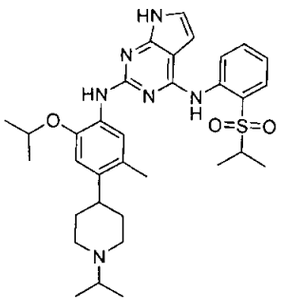
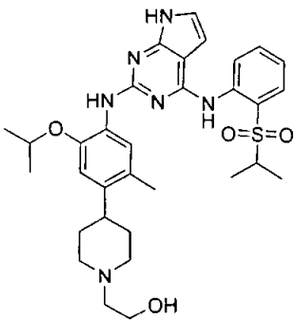
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
	carboxílico	1.15 (d, 6H). MS (ES^+): 511.1 $(M+1)^+$.
199	 4-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-6-metil-quinolina-2-carboxílico metilamida del ácido	^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.73 (s, 1H), 8.85 (s, 1H), 8.21-8.55 (m, 1H), 8.21 (s, 1H), 8.08-8.18 (m, 1H), 7.90-7.92 (d, 1H), 7.81-7.83 (dd, 1H), 7.51-7.67 (m, 4H), 7.18-7.21 (m, 1H), 3.13-3.16 (m, 1H), 3.03-3.05 (d, 3H), 1.23-1.25 (d, 3H). MS (ES^+): 525.7 $(M+1)^+$.
200	 4-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-quinolina-2-carboxílico ácido (2-morfolin-4-il-etil)-amida	^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.79 (s, 1H), 9.00 (s, 1H), 8.57-8.59 (m, 2H), 8.30 (s, 1H), 8.11-8.13 (d, 1H), 7.99-8.01 (d, 1H), 7.88-7.91 (dd, 1H), 7.20-7.78 (m, 4H), 7.24-7.26 (m, 1H), 3.78-3.80 (m, 4H), 3.64-3.69 (m, 2H), 3.20-3.23 (m, 1H), 2.67-2.71 (m, 2H), 2.58-2.60 (m, 2H), 1.25-1.31 (d, 3H). MS (ES^+): 610.7 $(M+1)^+$.
201	 [2-(4-metil-piperazin-1-il)-etil]-amida del ácido 4-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-quinolina-2-carboxílico	^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.73 (s, 1H), 8.93 (s, 1H), 8.43-8.52 (m, 2H), 8.22 (s, 1H), 8.03-8.05 (d, 1H), 7.93-7.95 (d, 1H), 7.82-7.84 (dd, 1H), 7.54-7.72 (m, 4H), 7.16-7.20 (m, 1H), 4.43-4.48 (m, 8H), 3.58-3.62 (m, 2H), 3.11-3.18 (m, 1H), 2.67-2.71 (m, 2H), 2.46 (s, 3H), 1.23-1.25 (d, 6H). MS (ES^+): 623.8 $(M+1)^+$.

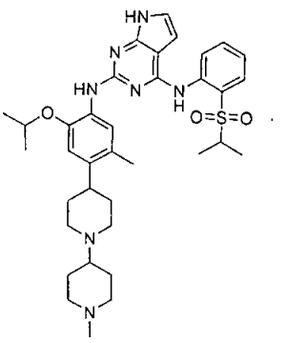
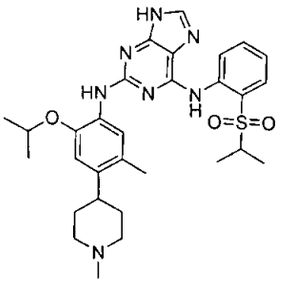
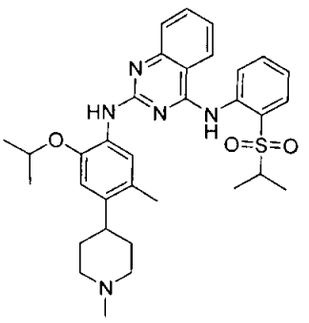
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
202	 piperidin-4-ilamida del ácido 4-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-quinolina-2-carboxílico	^{1}H NMR (CD_3OD, 400 MHz) δ 8.92 (s, 1H), 8.68-8.70 (d, 1H), 8.46-8.48 (m, 2H), 8.26-8.28 (d, 1H), 7.96-7.99 (m, 2H), 7.79-7.83 (t, 1H), 7.67-7.71 (t, 1H), 7.38-7.42 (t, 1H), 4.31-4.33 (m, 1H), 3.60-3.63 (m, 2H), 3.40-3.46 (m, 1H), 3.27-3.33 (m, 2H), 2.33-2.37 (m, 2H), 2.05-2.08 (m, 2H), 1.35-1.37 (d, 6H). MS (ES^+): 580.7 $(M+1)^+$.

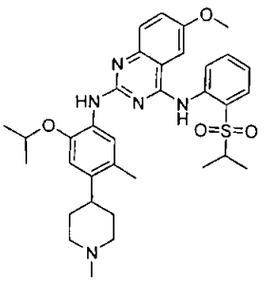
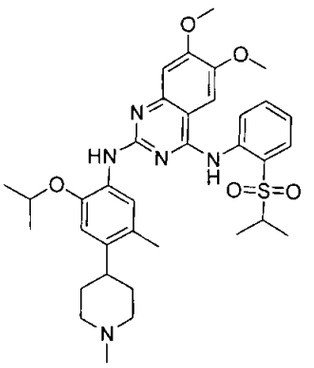
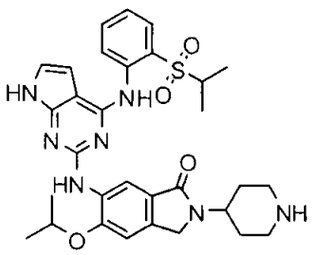
[0137] La Tabla 2 muestrun compuestos ilustrativos de Fórmula (1C).

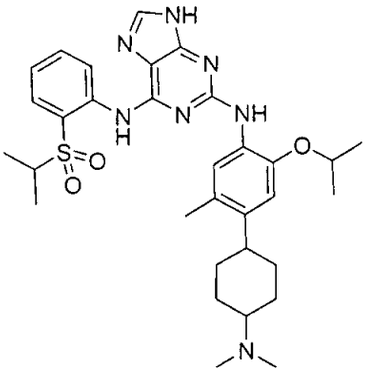
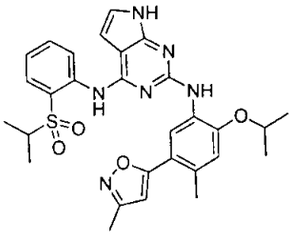
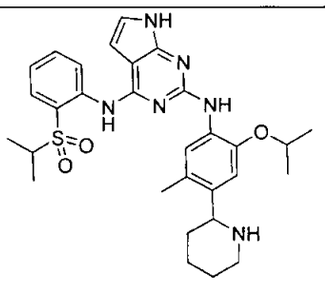
Tabla 2

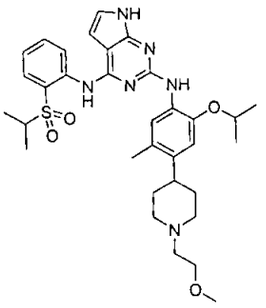
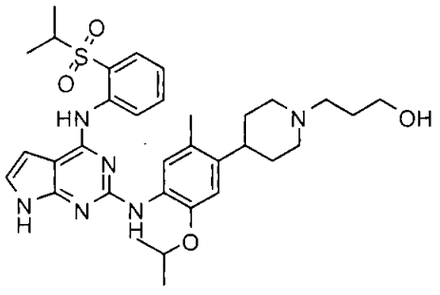
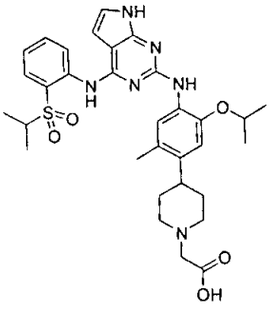
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
203	 N2-(2-isopropoxi-5-metil-4-(piperidin-4-il)fenil)-N4-(2-(metilsulfonil)fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina	MS (ES^+): 534.6 $(M+1)^+$
204	 N2-(4-(1-etilpiperidin-4-il)-2-isopropoxi-5-metilfenil)-N4-(2-(isopropilsulfonil)fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina	MS (ES^+): 590.8 $(M+1)^+$.

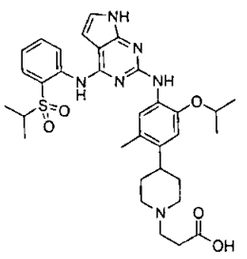
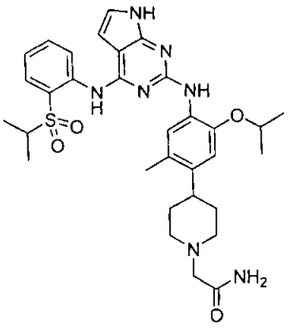
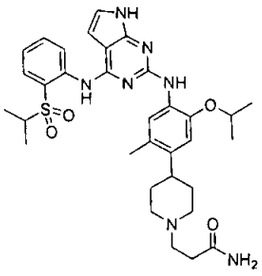
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
205	 2-(4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)piperidin-1-il)propan-1-ol	MS (ES^+): 620.3 $(M+1)^+$.
206	 N2-(2-isopropoxi-4-(1-isopropilpiperidin-4-il)-5-metilfenil)-N4-(2-(isopropilsulfonil)fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina	MS (ES^+): 604.8 $(M+1)^+$.
207	 2-(4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)piperidin-1-il)etanol	MS (ES^+): 606.8 $(M+1)^+$.

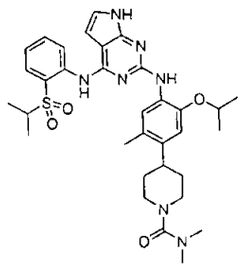
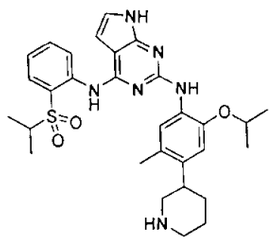
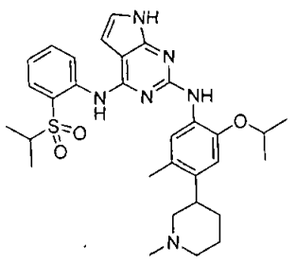
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
208	 N2-(2-isopropoxi-5-metil-4-(1'-metil-1,4'-bipiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil) fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina	MS (ES^+): 659.8 $(M+1)^+$.
209	 N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N6-(2-(isopropilsulfonil)fenil)-9H-purina-2,6-diamina	MS (ES^+): 577.7 $(M+1)^+$.
210	 N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)quinazolina-2,4-diamina	MS (ES^+): 588.7 $(M+1)^+$.

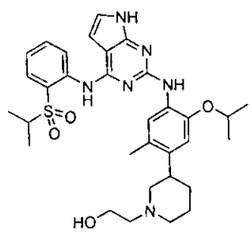
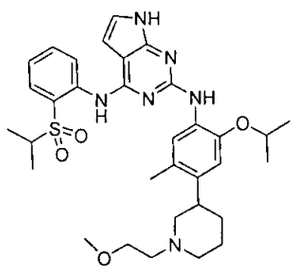
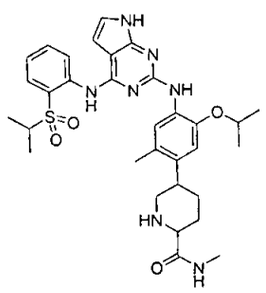
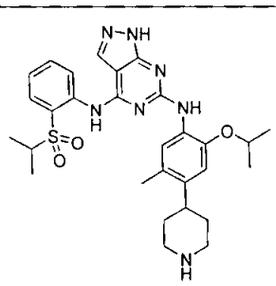
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
211	 N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-6-metoxiquinazolina-2,4-diamina	MS (ES^+): 618.8 $(M+1)^+$.
212	 N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-6,7-dimetoxiquinazolina-2,4-diamina	MS (ES^+): 648.8 $(M+1)^+$.
213	 5-isopropoxi-6-(4-(2-(isopropilsulfonil)fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-(piperidin-4-il)isoindolin-1-ona	MS (ES^+): 604.7 $(M+1)^+$.

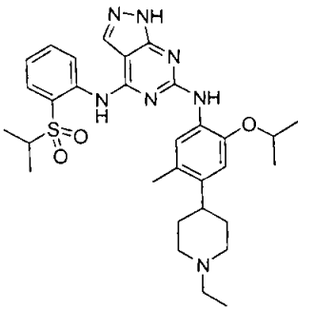
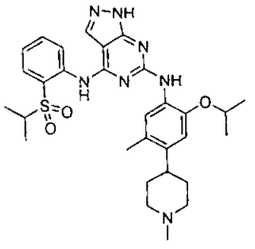
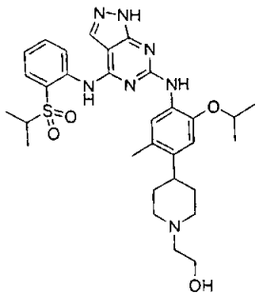
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
214	 N2-(4-(4-(dimetilamino)ciclohexil)-2-isopropoxi-5-metilfenil)-N6-(2-(isopropilsulfonil)fenil)-9H-purina-2,6-diamina	MS (ES^+): 606.7 $(M+1)^+$.
215	 N2-(2-isopropoxi-4-metil-5-(3-metilisoxazol-5-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina	MS (ES^+): 561.6 $(M+1)^+$.
216	 N2-(2-isopropoxi-5-metil-4-(piperidin-2-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina	MS (ES^+): 563.2 $(M+1)^+$.

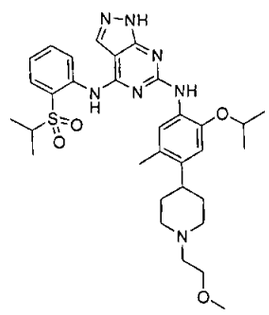
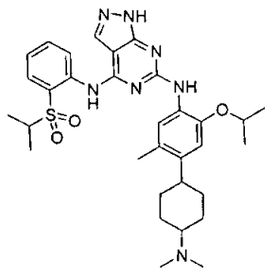
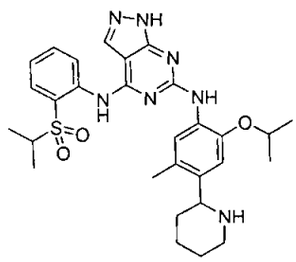
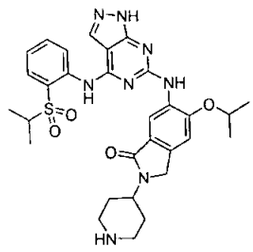
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
217	 N2-(2-isopropoxi-4-(1-(2-metoxietil)piperidin-4-il)-5-metilfenil)-N4-(2-(isopropilsulfonil)fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina	MS (ES^+): 621.8 $(M+1)^+$.
218	 3-(4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)piperidin-1-il)propan-1-ol	MS (ES^+): 621.8 $(M+1)^+$.
219	 ácido 2-(4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)piperidin-1-il)acético	MS (ES^+): 621.7 $(M+1)^+$.

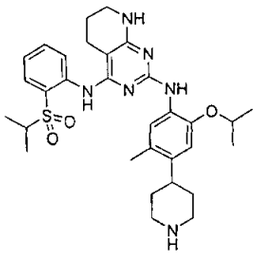
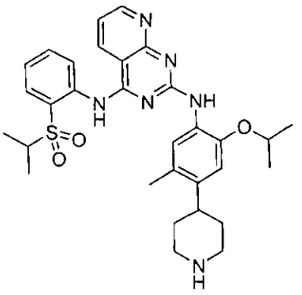
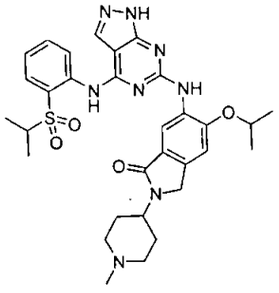
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
220	 ácido 3-(4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)piperidin-1-il)propanoico	MS (ES^+): 635.8 $(M+1)^+$.
221	 2-(4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)piperidin-1-il)acetamida	MS (ES^+): 620.2 $(M+1)^+$.
222	 3-(4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)piperidin-1-il)propanamida	MS (ES^+): 634.8 $(M+1)^+$.

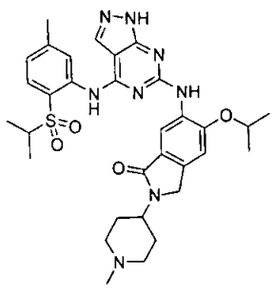
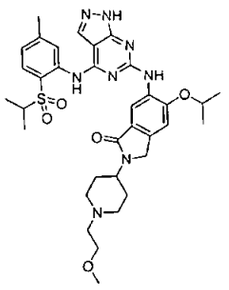
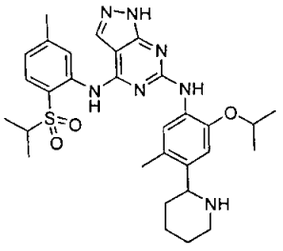
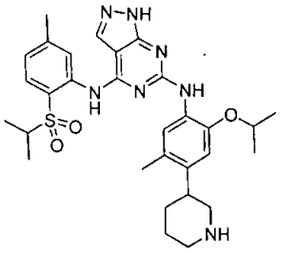
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
223	 4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)-N,N-dimetilpiperidina-1-carboxamida	MS (ES^+): 634.8 $(M+1)^+$.
224	 N2-(2-isopropoxi-5-metil-4-(piperidin-3-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina	MS (ES^+): 563.7 $(M+1)^+$.
225	 N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-3-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina	MS (ES^+): 576.7 $(M+1)^+$.

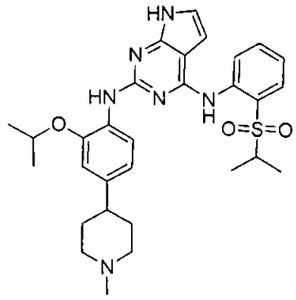
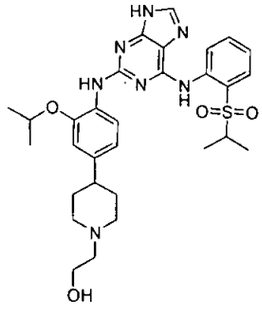
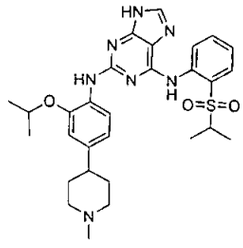
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
226	 2-(3-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)piperidin-1-il)etanol	MS (ES^+): 607.8 $(M+1)^+$.
227	 N2-(2-isopropoxi-4-(1-(2-metoxietil)piperidin-3-il)-5-metilfenil)-N4-(2-(isopropilsulfonil)fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina	MS (ES^+): 621.8 $(M+1)^+$.
228	 5-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)-N-metilpiperidina-2-carboxamida	MS (ES^+): 620.7 $(M+1)^+$.
229	 N6-(2-isopropoxi-5-metil-4-(piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidina-4,6-	MS (ES^+): 564.7 $(M+1)^+$.

	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
	diamina	
230	 N6-(4-(1-etilpiperidin-4-il)-2-isopropoxi-5-metilfenil)-N4-(2-(isopropilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidina-4,6-diamina	MS (ES^+): 592.7 $(M+1)^+$.
231	 N6-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidina-4,6-diamina	MS (ES^+): 578.7 $(M+1)^+$.
232	 2-(4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-1H-pirazolo[3,4-d]pirimidin-6-ilamino)-2-metilfenil)piperidin-1-il)etanol	MS (ES^+): 608.7 $(M+1)^+$.

	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
233	 N6-(2-isopropoxi-4-(1-(2-metoxietil)piperidin-4-il)-5-metilfenil)-N4-(2-(isopropilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidina-4,6-diamina	MS (ES^+): 622.7 $(M+1)^+$.
234	 N6-(4-(4-(dimetilamino)ciclohexil)-2-isopropoxi-5-metilfenil)-N4-(2-(isopropilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidina-4,6-diamina	MS (ES^+): 606.8 $(M+1)^+$.
235	 N6-(2-isopropoxi-5-metil-4-(piperidin-2-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidina-4,6-diamina	MS (ES^+): 564.7 $(M+1)^+$.
236		MS (ES^+): 605.7 $(M+1)^+$.

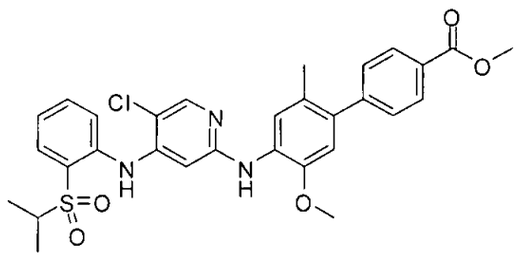
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
	5-isopropoxi-6-(4-(2-(isopropilsulfonil)fenilamino)-1H-pirazolo[3,4-d]pirimidin-6-ilamino)-2-(piperidin-4-il)isoindolin-1-ona	
237	 N2-(2-isopropoxi-5-metil-4-(piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-5,6,7,8-tetrahidropirido[2,3-d]pirimidina-2,4-diamina	MS (ES^+): 579.7 $(M+1)^+$.
238	 N2-(2-isopropoxi-5-metil-4-(piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirido[2,3-d]pirimidina-2,4-diamina	MS (ES^+): 575.7 $(M+1)^+$.
239	 5-isopropoxi-6-(4-(2-(isopropilsulfonil)fenilamino)-1H-pirazolo[3,4-d]pirimidin-6-ilamino)-2-(1-metilpiperidin-4-il)isoindolin-1-ona	MS (ES^+): 619.7 $(M+1)^+$.

	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
240	 5-isopropoxi-6-(4-(2-(isopropilsulfonil)-5-metilfenilamino)-1H-pirazolo[3,4-d]pirimidin-6-ilamino)-2-(1-metilpiperidin-4-il)isoindolin-1-ona	MS (ES^+): 633.7 $(M+1)^+$.
241	 5-isopropoxi-6-(4-(2-(isopropilsulfonil)-5-metilfenilamino)-1H-pirazolo[3,4-d]pirimidin-6-ilamino)-2-(1-(2-metoxietil)piperidin-4-il)isoindolin-1-ona	MS (ES^+): 677.8 $(M+1)^+$.
242	 N6-(2-isopropoxi-5-metil-4-(piperidin-2-il)fenil)-N4-(2-(isopropilsulfonil)-5-metilfenil)-1H-pirazolo[3,4-d]pirimidina-4,6-diamina	MS (ES^+): 578.7 $(M+1)^+$.
243	 N6-(2-isopropoxi-5-metil-4-(piperidin-3-il)fenil)-N4-(2-	MS (ES^+): 578.7 $(M+1)^+$.

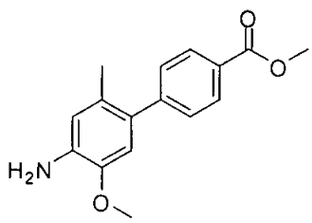
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
	(isopropilsulfonil)-5-metilfenil)-1H-pirazolo[3,4-d]pirimidina-4,6-diamina	
244	 N2-(2-isopropoxi-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina	MS (ES^+): 562.3 $(M+1)^+$.
245	 2-(4-(3-isopropoxi-4-(6-(2-(isopropilsulfonil) fenilamino)-9H-purin-2-ilamino)fenil)piperidin-1-il)etanol	MS (ES^+): 593.7 $(M+1)^+$.
246	 N2-(2-isopropoxi-4-(1-metilpiperidin-4-il)fenil)-N6-(2-(isopropilsulfonil)fenil)-9H-purina-2,6-diamina	MS (ES^+): 563.7 $(M+1)^+$.

Ejemplo 17

Metil 4'-(5-cloro-4-(2-(isopropilsulfonil)fenilamino)piridin-2-ilamino)-5'-metoxi-2'-metilbifenil-4-carboxilato (**254**)

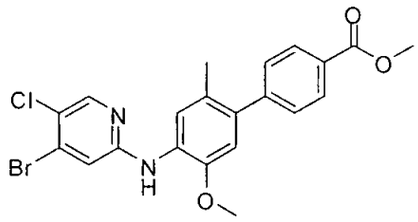


Paso 1: Metil 4'-amino-5'-metoxi-2'-metilbifenil-4-carboxilato



[0138] Metil 4'-amino-5'-metoxi-2'-metilbifenil-4-carboxilato; MS m/z 272.1 (M+1), puede ser sintetizado siguiendo los procedimientos anteriormente descritos **(Ejemplo 7, Pasos 1 y 2)** usando reactivos apropiados.

Paso 2: Metil 4'-(4-bromo-5-cloropiridin-2-ilamino)-5'-metoxi-2'-metilbifenil-4-carboxilato



[0139] Metil 4'-amino-5'-metoxi-2'-metilbifenil-4-carboxilato generado en el Paso 1 (200 mg, 0.75 mmol), 2,4-dibromo-5-cloropiridina (222 mg, 0.82 mmol, 1.1 equiv), $Pd_2(dba)_3$ (17 mg, 0.02 mmol, 0.025 equiv.), xantfos (22 mg, 0.04 mmol, 0.05 equiv.), y Cs_2CO_3 (365 mg, 1.1 mmol, 1.5 equiv.) son adicionados a THF (5 mL). La mezcla resultante es burbujeada con gas N_2 por 5 minutos y luego calentada a 150 °C por 4 horas. Luego de enfriarse a temperatura ambiente, la mezcla de reacción es diluida into EtOAc y lavada con H_2O. La capa de EtOAc se seca sobre Mg_2SO_4 y se concentra al vacío. Cromatografía de silica gel (hexanos-EtOAc)

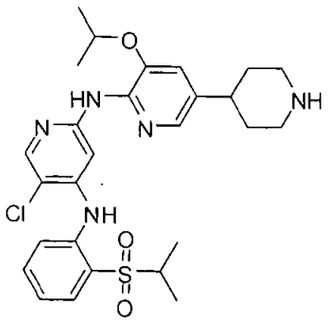
proporciona Metil 4'-(4-bromo-5-cloropiridin-2-ilamino)-5'-metoxi-2'-metilbifenil-4-carboxilato; MS m/z 461.0 (M+1).

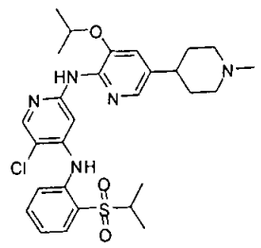
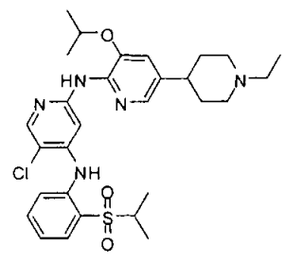
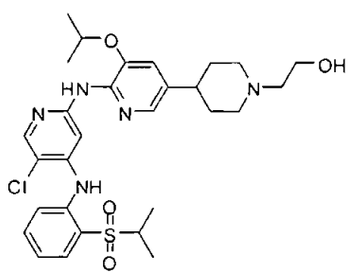
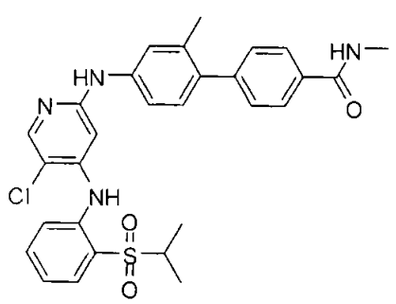
Paso 3: Metil 4'-(5-cloro-4-(2-(isopropilsulfonil)fenilamino)piridin-2-ilamino)-5'-metoxi-2'-metilbifenil-4-carboxilato (254)

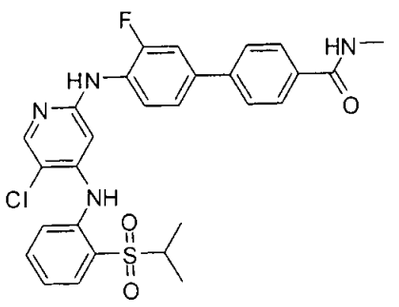
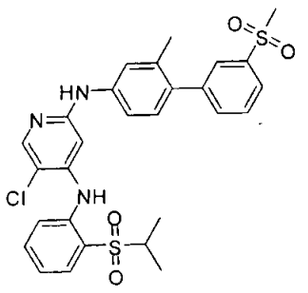
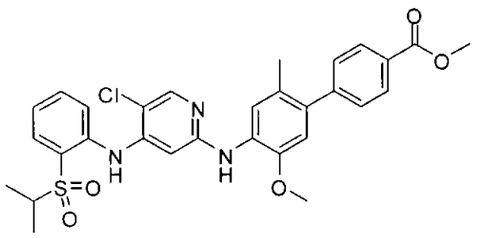
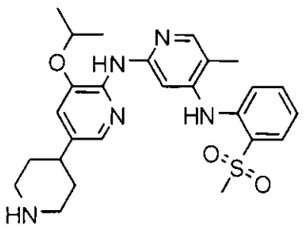
[0140] Metil 4'-(4-bromo-5-cloropiridin-2-ilamino)-5'-metoxi-2'-metilbifenil-4-carboxilato generado en el Paso 2 (9 mg, 0.022 mmol), 2-(isopropilsulfonil)anilina (4 mg, 0.022 mmol, 1 equiv). $Pd_2(dba)_3$ (1.7 mg, 0.002 mmol, 0.1 equiv.), 2-(Diciclohexilfosfino)-2',4',6'-tri-i-propil-1,1`-bifenil (1.8 mg, 0.004 mmol, 0.2 equiv.), y Sodio tert-butoxido (2.7 mg, 0.028 mmol, 1.3 equiv.) son adicionados a THF (1 mL). La mezcla resultante es burbujeada con gas N_2 por 5 minutos y luego calentada a 150 °C por 4 horas. Luego de enfriarse a temperatura ambiente, La mezcla de reacción es diluida en EtOAc y lavada con H_2O. La capa de EtOAc se seca sobre Mg_2SO_4 y se concentra al vacío. Cromatografía de silica gel (hexanos-EtOAc) proporciona Metil 4'-(5-cloro-4-(2-(isopropilsulfonil)fenilamino)piridin-2-ilamino)-5'-metoxi-2'-metilbifenil-4-carboxilato (**254**); MS m/z 580.2 (M+1).

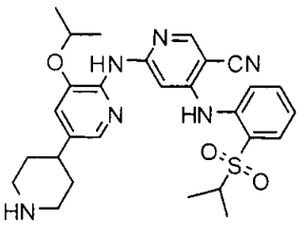
[0141] Compuestos ilustrativos de la invención se muestran a continuación. La Tabla 3 muestra compuestos ilustrativos de Fórmula (5).

Tabla 3

	Estructura	**Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)**
247	 5-cloro-N2-(3-isopropoxi-5-(piperidin-4-il)piridin-2-il)-N4-(2-(isopropilsulfonil)fenil)piridina-2,4-diamina	MS (ES^+): 544.2 $(M+1)^+$.

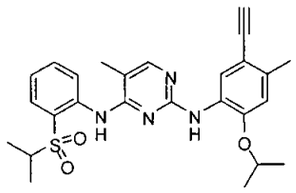
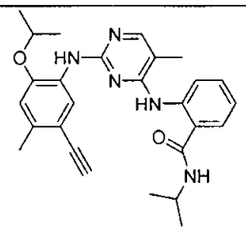
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
248	 5-cloro-N2-(3-isopropoxi-5-(1-metilpiperidin-4-il)piridin-2-il)-N4-(2-(isopropilsulfonil) fenil)piridina-2,4-diamina	MS (ES^+): 558.2 $(M+1)^+$.
249	 5-cloro-N2-(5-(1-etilpiperidin-4-il)-3-isopropoxipiridin-2-il)-N4-(2-(isopropilsulfonil) fenil)piridina-2,4-diamina	MS (ES^+): 572.2 $(M+1)^+$.
250	 2-(4-(6-(5-cloro-4-(2-(isopropilsulfonil) fenilamino)piridin-2-ilamino)-5-isopropoxipiridin-3-il)piperidin-1-il)etanol	MS (ES^+): 588.2 $(M+1)^+$.
251	 4'-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) piridin-2-ilamino)-N,2'-dimetilbifenil-4-carboxamida	MS (ES^+): 549.2 $(M+1)^+$.

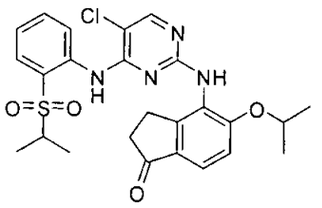
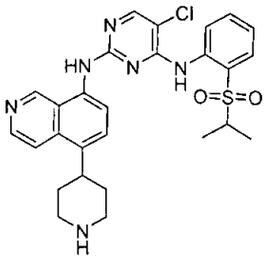
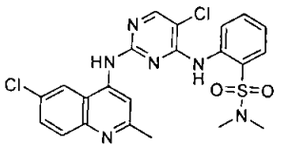
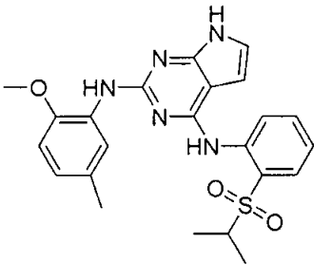
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
252	 4'-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) piridin-2-ilamino)-3'-fluoro-N-metilbifenil-4-carboxamida	MS (ES^+): 553.1 $(M+1)^+$.
253	 5-cloro-N4-(2-(isopropilsulfonil)fenil)-N2-(2-metil-3'-(metilsulfonil)bifenil-4-il)piridina-2,4-diamina	MS (ES^+): 570.1 $(M+1)^+$.
254	 Metil 4'-(5-cloro-4-(2-(isopropilsulfonil) fenilamino)piridin-2-ilamino)-5'-metoxi-2'-metilbifenil-4-carboxilato	MS m/z 580.2 $(M+1)^+$.
255	 N2-(3-isopropoxi-5-(piperidin-4-il)piridin-2-il)-5-metil-N4-(2-(metilsulfonil)fenil)piridina-2,4-diamina	MS (ES^+): 495.6 $(M+1)^+$.

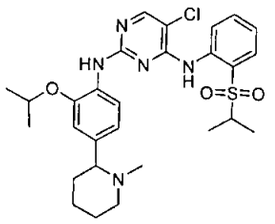
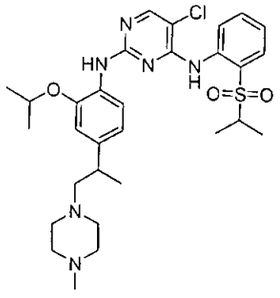
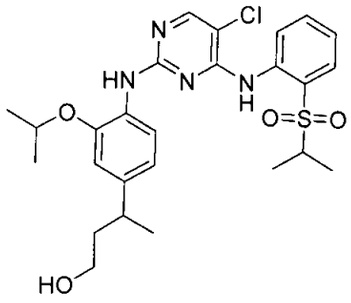
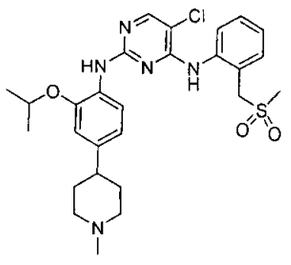
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS. (m/z)
256	 6-(3-isopropoxi-5-(piperidin-4-il)piridin-2-ilamino)-4-(2-(isopropilsulfonil)fenilamino) nicotinonitrilo	MS (ES^+): 534.6 $(M+1)^+$.

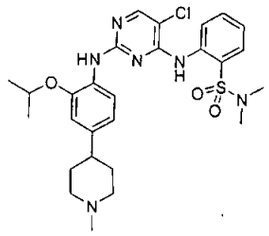
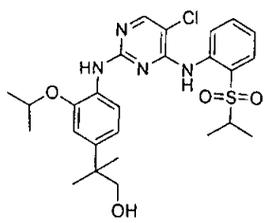
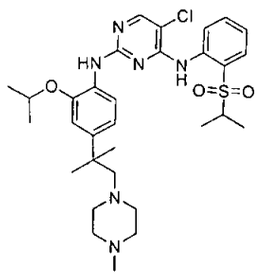
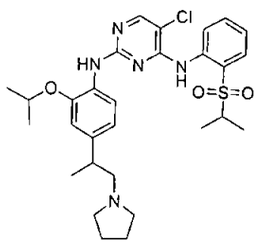
[0142] Tabla 4 muestra otros compuestos que pueden se útlies en el tratamiento, alivo o prevención de una condición que responda a la inhibición de la actividad de la quinasa del linfoma anaplásico ALK), quinasa de adhesión focal (FAK), proteína quinasa 70 asociada a la cadena zeta (ZAP-70), factor de crecimiento tipo insulina (IGF-1R).

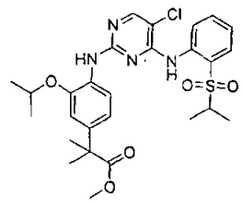
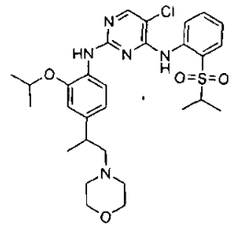
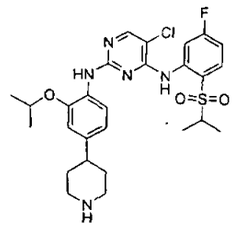
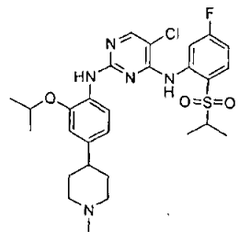
Tabla 4

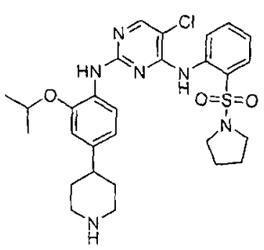
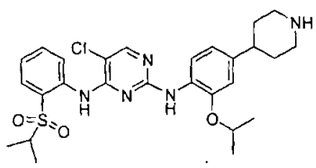
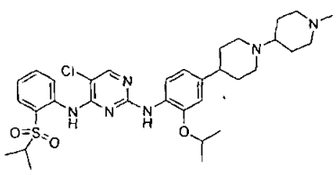
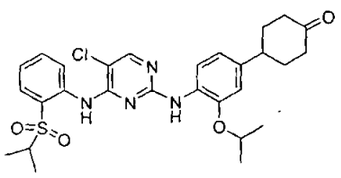
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
257	 N2-(5-Etinil-2-isopropoxi-4-metil-fenil)-5-metil-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina	MS (ES^+): 479.2 $(M+1)^+$.
258	 2-(2-(5-etinil-2-isopropoxi-4-metilfenilamino)-5-metilpirimidin-4-ilamino)-N-isopropilbenzamida	MS (ES^+): 458.6 $(M+1)^+$.

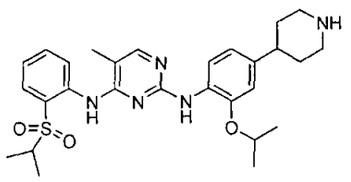
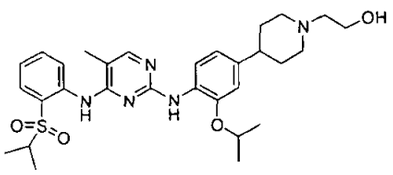
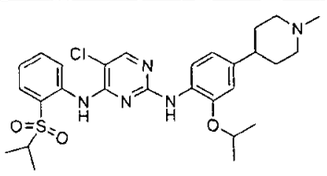
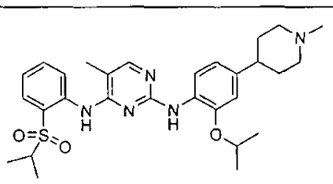
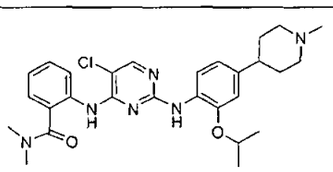
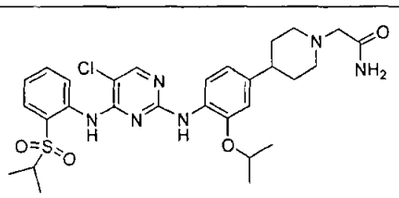
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
259	 4-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2,3-dihidro-5-isopropoxiinden-1-ona	MS (ES^+): 515.1 $(M+1)^+$.
260	 5-cloro-N4-(2-(isopropilsulfonil)fenil)-N2-(5-(piperidin-4-il)isoquinolin-8-il)pirimidina-2,4-diamina	MS (ES^+): 537.1 $(M+1)^+$.
261	 2-[5-Cloro-2-(6-cloro-2-metil-quinolin-4-ilamino)-pirimidin-4-ilamino]-N,N-dimetil-bencenosulfonamida	^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.45 (s, 1H), 8.34-8.37 (d, 1H), 8.20 (s, 1H), 8.10 (s, 1H), 7.82-7.9 (m, 3H), 7.52-7.60 (m, 3H), 7.19-7.26 (m, 1H), 2.69 (s. 6H), 2.54 (s, 3H). MS (ES^+): 503.0 $(M+1)^+$.
262	 N4-(2-(isopropilsulfonil)fenil)-N2-(2-metoxi-5-metilfenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina	MS (ES^+): 451.5 $(M+1)^+$.

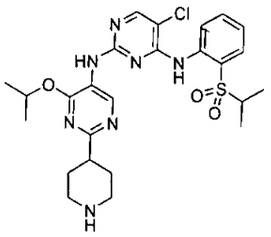
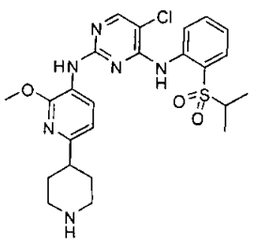
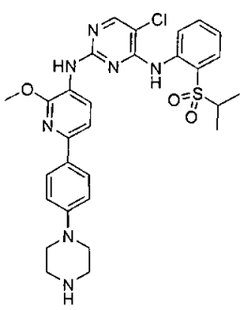
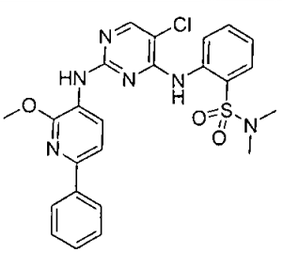
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
263	 5-cloro-N2-(2-isopropoxi-4-(1-metilpiperidin-2-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES^+): 558.1 $(M+1)^+$.
264	 5-cloro-N2-(2-isopropoxi-4-(1-(4-metilpiperazin-1-il)propan-2-il)fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina	MS (ES^+): 601.2 $(M+1)^+$.
265	 3-(4-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) pirimidin-2-ilamino)-3-isopropoxifenil)butan-1-ol	MS (ES^+): 533.1 $(M+1)^+$.
266	 5-cloro-N2-(2-isopropoxi-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(metilsulfonilmetil) fenil)pirimidina-2,4-diamina	MS (ES^+): 544.1 $(M+1)^+$.

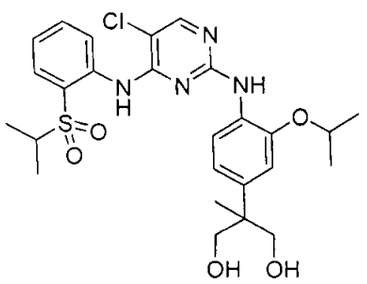
	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
267	 2-(5-cloro-2-(2-isopropoxi-4-(1-metilpiperidin-4-il)fenilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida	MS (ES^+): 559.1 $(M+1)^+$.
268	 2-(4-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) pirimidin-2-ilamino)-3-isopropoxifenil)-2-metilpropan-1-ol	MS (ES^+): 533.1 $(M+1)^+$.
269	 5-cloro-N2-(2-isopropoxi-4-(2-metil-1-(4-metilpiperazin-1-il)propan-2-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES^+): 615.3 $(M+1)^+$.
270	 5-cloro-N2-(2-isopropoxi-4-(1-(pirrolidin-1-il)propan-2-il)fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina	MS (ES^+): 572.2 $(M+1)^+$.

	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
271	 Metil 2-(4-(5-cloro-4-(2-(isopropilsulfonil) fenilamino)pirimidin-2-ilamino)-3-isopropoxifenil)-2-metilpropanoato	MS (ES^+): 561.1 $(M+1)^+$.
272	 5-cloro-N2-(2-isopropoxi-4-(1-morfolinopropan-2-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES^+): 588.2 $(M+1)^+$.
273	 5-cloro-N4-(5-fluoro-2-(isopropilsulfonil)fenil)-N2-(2-isopropoxi-4-(piperidin-4-il)fenil)pirimidina-2,4-diamina	MS (ES^+): 562.1 $(M+1)^+$.
274	 5-cloro-N4-(5-fluoro-2-(isopropilsulfonil)fenil)-N2-(2-isopropoxi-4-(1-metilpiperidin-4-il)fenil)pirimidina-2,4-diamina	MS (ES^+): 576.2 $(M+1)^+$.

	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
275	 5-cloro-N2-(2-isopropoxi-4-(piperidin-4-il)fenil)-N4-(2-(pirrolidin-1-ilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES$^+$): 571.1 (M+1)$^+$.
276	 5-cloro-N2-(2-isopropoxi-4-(piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES$^+$): 544.1 (M+1)$^+$.
277	 5-cloro-N2-(2-isopropoxi-4-(1-(1-metilpiperidin-4-il)piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES$^+$): 641.3 (M+1)$^+$.
278	 4-(4-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-3-isopropoxifenil)ciclohexanona	MS (ES$^+$): 557.1 (M+1)$^+$.

	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
279	 N2-(2-isopropoxi-4-(piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-5-metilpirimidina-2,4-diamina	MS (ES^+): 524.2 $(M+1)^+$.
280	 2-(4-(4-(4-(2-(isopropilsulfonil)fenilamino)-5-metilpirimidin-2-ilamino)-3-isopropoxi fenil)piperidin-1-il)etanol	MS (ES^+): 568.7 $(M+1)^+$.
281	 5-cloro-N2-(2-isopropoxi-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina	MS (ES^+): 558.1 $(M+1)^+$.
282	 N2-(2-isopropoxi-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-5-metilpirimidina-2,4-diamina	MS (ES^+): 538.7$(M+1)^+$.
283	 2-(2-(2-isopropoxi-4-(1-metilpiperidin-4-il)fenilamino)-5-cloropirimidin-4-ilamino)-N,N-dimetilbenzamida	MS (ES^+): 523.0 $(M+1)^+$.
284	 2-(4-(4-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-	MS (ES^+): 601.1 $(M+1)^+$.

	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
	ilamino)-3-isopropoxifenil) piperidin-1-il)acetamida	
285	 5-cloro-N2-(4-isopropoxi-2-(piperidin-4-il)pirimidin-5-il)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina	MS (ES$^+$): 546.1 $(M+1)^+$.
286	 5-cloro-N4-(2-(isopropilsulfonil)fenil)-N2-(2-metoxi-6-(piperidin-4-il)piridin-3-il) pirimidina-2,4-diamina	MS (ES$^+$): 517.1 $(M+1)^+$.
287	 5-cloro-N4-(2-(isopropilsulfonil)fenil)-N2-(2-metoxi-6-(4-(piperazin-1-il)fenil)piridin-3-il)pirimidina-2,4-diamina	MS (ES$^+$): 594.1 $(M+1)^+$.
288	 2-(5-cloro-2-(2-metoxi-6-fenilpiridin-3-ilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida	MS (ES$^+$): 511.1 $(M+1)^+$.

	Estructura	Información física ^{1}H NMR 400 MHz (DMSO-d6) y/o MS (m/z)
289	 2-(4-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) pirimidin-2-ilamino)-3-isopropoxifenil)-2-metilpropano-1,3-diol	MS (ES^+): 548.1 $(M+1)^+$.

[0143] Compuestos de la presente invención pueden ser ensayados en su habilidad para inhibir ALK usando lso ensayos descritos a continuación, así como otros ensayos conocidos en el arte.

Panel de la línea cellular Ba/F3 y reactivos

[0144] La Ba/F3 es una línea celular IL-3 linfoma de murina dependiente de pro-B. Las células parentales de Ba/F3 se utilizan para generar un panel de sublíneas cuya proliferación y la supervivencia se hace independiente de IL-3 por transducción estable con tirosin quinasas individuales activadas por la fusión con la porción amino-terminal de TEL (aminoácidos 1-375) de BCR. Con el fin de generar líneas célulares transformadas Ba/F3 por fusiones de Tel-tirosina quinasa (TK), las células parentales Ba/F3 se infectan con un retrovirus que alberga cada dominio de quinasa y se someten a selección puromicina y retiro de IL-3 para obtener células Ba/F3 transformado independientes de IL-3.

[0145] Cada célula transformada Ba/F3 se cultiva en medio RPMI-1640 (Gibco Cat #11875093, Carlsbad, CA) enriquecido con 10% FBS (Hyclone Cat #SV30014.03, Logan, UT), 4.5 g/L glucosa (Sigma #G5400, St.Louis, MO), 1.5 g/L bicarbonato de sodio (Biowhittaker #17-613E, Walkersville, MD) y Pen/Strep (Gibco #10378-016, Carlsbad, CA). Las células son separados dos veces a la semana.

Ensayo de viavilidad de inhibición de células Ba/F3

[0146]

La potencia de los compuestos de prueba contra diversas líneas Ba/F3 Tel-TK transformadas se determina de la siguiente manera. Células BaF3 Tel-TK en crecimiento exponencial se diluyen

en medio fresco a 75.000 células / ml y son sembradas en placas de 384 pozos (3750 células / pozo) a 50 µL / pozo y usando un dispensador de líquidos µFill (Biotek, Winooski, Vermont, EE.UU.). Placas duplicadas se corren para cada línea celular. Los compuestos de prueba y control son diluidos en serie con DMSO y dispuestos en una placa-384 de polipropileno. 50nL de compuestos se transfiere a las placas de ensayo de utilizando un dispositivo de transferencia, y las placas se incuban a 37 ° C (5% de CO_2) durante 48 horas. Se agregan 25 µL de Bright -Glo (Promega, Madison, WI, EE.UU.) y se cuantifica la luminiscencia usando un analyst-GT (Perkin Elmer, Wellesley, MA). Software de ajuste personalizado de curva se utiliza para producir un ajuste logístico en porcentage de la viabilidad celular en función del logaritmo de la concentración de inhibidor. La IC_{50} es interpolada como la concentración de los compuestos necesaria para reducir la viabilidad celular en un 50% de un control DMSO. Las células parentales Ba/F3 que se mantienen en cultivo y en presencia de IL-3 (1 ng / ml en final) se diluyen en un medio fresco que contiene la IL-3 (1 ng / ml en la final), a 75.000 células / ml siguiendo el mismo procedimiento como se ha descrito anteriormente

Ensayo celular Kapas 299

[0147] Las Karpas 299 luciferizadas (Karpas299-Luc) son generadas por retrovirus infecciosos que codifican genes de luciferasa, y son cultivadas en medio RPMI-1649 suplementado con 10% FBS, 1% P/S/L-Glu. En el día 1, las células se cosechan y son resuspendidas a una densidad de 150.000 células / ml (el número de células se mide utilizando ViCell (BD). Las células se dispensan de una suspensión diluida en una Placa-384 de ensayo y en un volumen de 50 µl usando un µFill (Bio-TEK). Diluciones seriales de los compuestos (en DMSO) se transfieren a la placa usando un pinhead de 50 nL. Las placas se incuban a 37°C durante 48 horas. En el día 4, 25 µl/pozo de reactivo Bright-Glo (Promega) se añade (Bio-TEK). Dentro de los 30 minutos, la señal se mide usando un analyst-GT en configuración predeterminada para la detección de luminiscencia.

Ensayo enzimático HTRF

[0148] Se compran la enzima ALK e IGF1R e INSR de Upstate. Los siguientes reactivos se preparan localmente; buffer 10 x kinas (KB) (200 mM Tris (pH 7.0), 100 mM $MgCl_2$, 30 mM $MnCl_2$, 50 nM $NaVO_4$), 10 mM ATP, 100 mg/ml BSA, 0.5 M EDTA, 4 M KF. Proxiplate-384 de Perkin-Elmer es usado para la preparación del ensayo. Todos los reactivos HTRF incluyendo el sustrato (Biotin-poly-GT (61GT0BLB), Mab PT66-K, (61T66KLB), Streptavidin-XL^{ent} (611SAXLB)) se compran de CIS-US, Inc.

[0149] La mezcla de substrato/ATP se prepara por adición de ATP (concentración final, 3 µM) y poli-GT biotinizado (concentración final, 10 ng/µl) en 1x KB, que se dispensa en una placa Proxiplate-384 a 5 µl/pozo usando un µFill (Bio-TEK). Compuestos en diluciones seriales (en DMSO) se transfieren a la placa usando un pinhead de 50 nL. 5 µL de la mezcla enzimática preparada (enzima (concentración final, 5 ng/µl), se mezcla con BSA y DTT en 1x KB) se agrega para iniciar la reacción de quinasa usando un µFill (Bio-TEK). La placa de ensayo se incuba a temperatura ambiente por 2 horas. La mezcla de detección se prepara por adición de Mab PT66-K y Streptavidin-XL^{ent} en una solución 0.5 x KB que contiene KF (concentración final, 125 mM), EDTA (concentración final, 50 mM) y BSA (concentración final, 100 µg/ml). Al final de la reacción, se agregan 10 µL de mezcla de detección y se incuba por 30 minutos a temperatura ambiente antes de la medición. Se detecta la señal HTRF usando un Analyst-GT (molecular dynamic).

Ensayo reportero en células U2OS usando RE1-pGL3 por IGF1-S3-5 o INSR-S3-5

[0150] Céluas semilla 10M / T175 frasco en Mc Coy 10% FBS y 4 días después, se succiona el medio y se adiciona medio fresco. Al siguiente día (5 días después de la siembra), células tripsinizadas, se lavan una vez con PBS, luego se resuspenden las células en medio Mc-Coy 4% suero sin lípidos con P/S/G. Las células se cuentan y se diluyen a 400,000 células/ml.

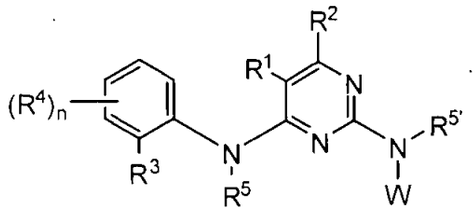
[0151] Para 95 ml de células (400000 células/ml (40M)), se prepara la siguiente mezcla de DNA/Fugene6: 5 ml Mc-Coy medio sin suero; 120 µg DNA mix (20 µg IGF1R-S3-5 o INSR-S3-5+100 µg RE1-pGL3); y 240 µL de reactivo Fugene6. Se incuba la mezcla DNA/ Fugene 6 por 15 min antes de añadirla a las células en 4% de suero sin lípidos. Se dispensan 50 µL/pozo en una placa-384. 22-24h después, se adiciona 50 nL de compuestos serialmente diluidos usando el pinhead. 30 min después, se adiciona una dosis de 2 µL de 26X IGF1 (o 100X insulina) diluido en Mc-Coy 4% suero sin lípidos usando µ-Fill. 30 horas después, se adicionan 25 µL 100% bright-glo y se leen en un analyst-GT para medir la luminescencia.

[0152] Se entiende que los ejemplos y las modalidades que se describe en este documento sólo tienen fines ilustrativos y que diversas modificaciones o cambios a la luz de éstas son sugeridas a las personas medianamente versadas en la materia técnica son incluidas en el espíritu y alcance de esta solicitud y ámbito de aplicación de las reivindicaciones adjuntas. Todas las publicaciones, las patentes y solicitudes de patente citados en este documento se incorporan por referencia

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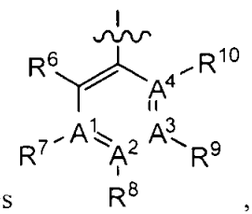
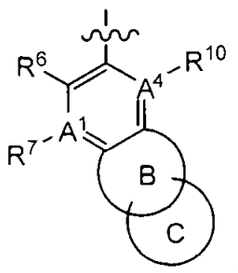
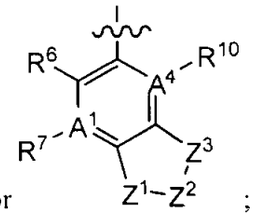
Claims

1. Un compuesto que tiene la Fórmula (1):



(1)

o sales farmacéuticamente aceptables del mismo; donde

W es  ,  or  ;

A^1 y A^4 son independientemente C o N;

cada A^2 y A^3 es C, o uno de A^2 y A^3 es N donde R^6 y R^7 forman un anillo;

B y C son independientemente un anillo carbocíclico de 5-7 miembros opcionalmente sustituido, aril, heteroaril o un anillo heterocíclico que contiene N, O o S;

Z^1, Z^2 y Z^3 son independientemente NR^{11}, C=O, CR-OR, $(CR_2)_{1-2}$ o =C-R^{12};

R^1 y R^2 son independientemente halo, OR^{12}, $NR(R^{12})$, SR^{12}, o un C_{1-6} alquil, C_{2-6} alquenil o C_{2-6} alquinil, opcionalmente sustituidos; o uno de R^1 y R^2 es H;

R^3 es $(CR_2)_{0-2}SO_2R^{12}$, $(CR_2)_{0-2}SO_2NRR^{12}$, $(CR_2)_{0-2}CO_{1-2}R^{12}$, $(CR_2)_{0-2}CONRR^{12}$ o ciano;

R^4, R^6, R^7 y R^{10} son independientemente un C_{1-6} alquil, C_{2-6} alquenil o C_{2-6} alquinil, opcionalmente sustituidos; OR^{12}, $NR(R^{12})$, halo, nitro, SO_2R^{12}, $(CR_2)_nR^{13}$ o X; o R^4, R^7 y R^{10} son independientemente H;

R, R^5 y $R^{5'}$ son independientemente H o C_{1-6} alquil;

R^8 y R^9 son independientemente C_{1-6} alquil, C_{2-6} alquenil, C_{2-6} alquinil, halo o X, o uno de R^8 y R^9 es H donde R^1 y R^2 forman un anillo; y siempre que uno de R^8 y R^9 es X;

alternativamente, R^1 y R^2, o R^6 y R^7, R^7 y R^8, o R^9 y R^{10}, cuyo están unidos a un átomo de carbono puede formar un anillo carbocíclico monocíclico o fusionado de 5-7

miembros opcionalmente sustituido, aril, o heteroaril o un anillo heterocíclico que comprende N, O y/o S; o R^7, R^8, R^9 y R^{10} están ausentes cuyo están unidos a un N;

R^{11} es H, C_{1-6} alquil, C_{2-6} alquenil, $(CR_2)_pCO_{1-2}R$, $(CR_2)_pOR$, $(CR_2)_pR^{13}$, $(CR_2)_pNRR^{12}$, $(CR_2)_pCONRR^{12}$ o $(CR_2)_pSO_{1-2}R^{12}$;

R^{12} y R^{13} son independientemente un anillo carbocíclico de 3-7 miembros saturado o parcialmente insaturado opcionalmente sustituido, o un anillo heterocíclico de 5-7 miembros que comprende N, O y/o S; aril o heteroaril; o R^{12} es H, C_{1-6} alquil;

X es $(CR_2)_qY$, ciano, $CO_{1-2}R^{12}$, $CONR(R^{12})$, $CONR(CR_2)_pNR(R^{12})$, $CONR(CR_2)_pOR^{12}$, $CONR(CR_2)_pSR^{12}$, $CONR(CR_2)_pS(O)_{1-2}R^{12}$ o $(CR_2)_{1-6}NR(CR_2)_pOR^{12}$;

Y es un anillo carbocíclico de 3-12 miembros opcionalmente sustituido, un aril de 5-12 miembros, o un heteroaril de 5-12 miembros o un anillo heterocíclico que comprende N, O y/o S y unido, a un^2 o A^3 o ambos por medio de un átomo de carbono de dicho heteroaril o un anillo heterocíclico donde q en $(CR_2)_qY$ es 0; y

n, p y q son independientemente 0-4.

2. El compuesto de la Reivindicación 1, donde R^1 es halo o C_{1-6} alquil;

R^2 es H o NH_2; o

R^1 y R^2 juntos forman un anillo de 5-6 miembros arílico, o heteroarílico o heterocíclico opcionalmente sustituido, que comprende 1-3 átomos de nitrógeno.

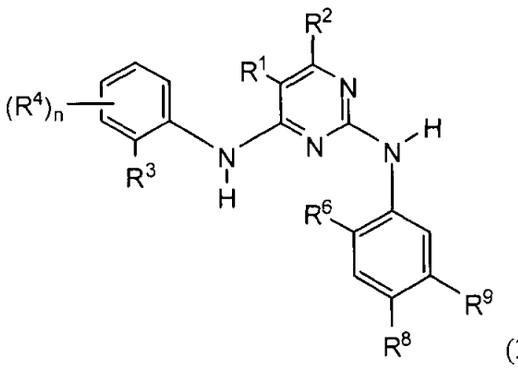
3. El compuesto de la Reivindicación 1 o la Reivindicación 2, donde R^3 es SO_2R^{12}, SO_2NH_2, SO_2NRR^{12}, CO_2NH_2, $CONRR^{12}$, $CO_{1-2}R^{12}$, o ciano; y

R^{12} es C_{1-6} alquil, un C_{3-7} cicloalquil, C_{3-7} cicloalquenil, pirrolidinil, piperazinil, piperidinil, morfolinil o azetidinilm, opcionalmente sustituidos.

4. El compuesto de cualquiera de las Reivindicaciones 1-3, donde R^5, $R^{5'}$, R^7 y R^{10} son independientemente H, y n es 0.

5. El compuesto de cualquiera de las Reivindicaciones 1-3, donde R^6 es OR^{12}, y R^{12} es C_{1-6} alquil.

6. El compuesto de cualquiera de las Reivindicaciones 1-3, donde dicho compuesto es de Fórmula (2):



(2)

donde R^1 es halo o C_{1-6} alquil;

R^2 es H; o

R^1 y R^2 juntos forman un anillo heteroarilo o heterocíclico de 5-6 miembros opcionalmente sustituido que comprende uno o dos átomos de nitrógeno;

R^6 es isopropoxi o metoxi;

uno de R^8 y R^9 es $(CR_2)_qY$ y el otro es C_{1-6} alquil, ciano, $CO_{1-2}R^{12}$, $CONR(R^{12})$ o $CONR(CR_2)_pNR(R^{12})$;

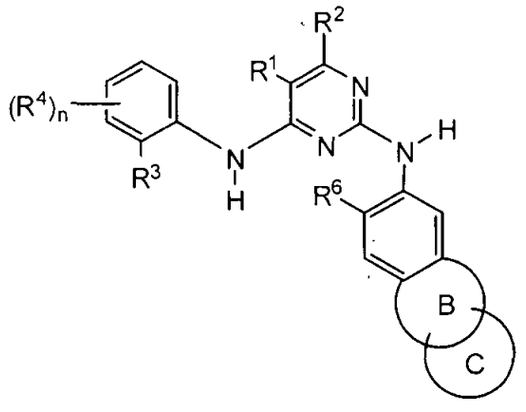
Y es un C_{3-7} cicloalquil, C_{3-7} cicloalquenil, o fenil, opcionalmente sustituidos; o Y es piridil, pirazolil, isoxazolil, imidazolil, tiazolil, benzimidazolil, pirrolidinil, piperazinil, piperidinil, morfolinil, azetidinil, heptametileneimina o octametileneimina, cada uno de los cuales está unidos al anillo fenil por medio de un átomo de carbono donde q en $(CR_2)_qY$ es 0;

n es 0-1; y

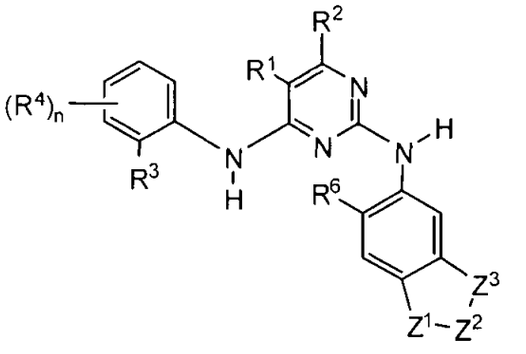
q es 0-4.

7. El compuesto de la Reivindicación 6, donde uno de R^8 y R^9 es $(CR_2)_qY$ y el otro es C_{1-6} alquil; y n y q son independientemente 0.

8. El compuesto de la Reivindicación 1, donde dicho compuesto es de Fórmula (3A) o (3B):

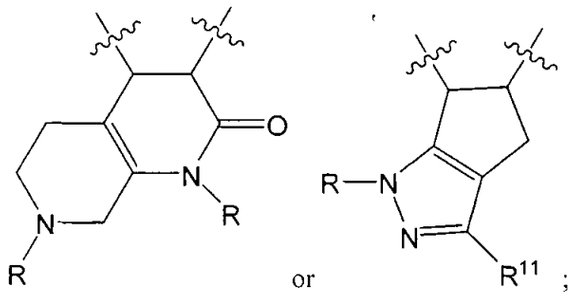


(3A)

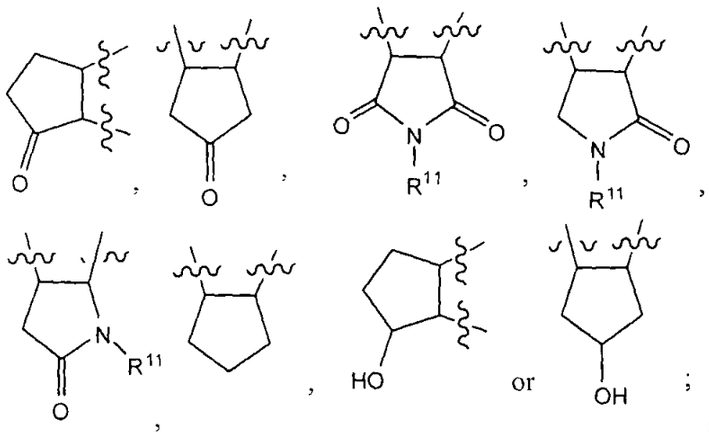


(3B)

donde B y C juntos forman



; Z^1, Z^2 y Z^3 juntos forman



o tautómeros de los mismos;

R^1 es halo o C_{1-6} alquil;

R^2 es H; o

R^1 y R^2 juntos forman un anillo carbocíclico de 5-7 miembros opcionalmente sustituido, aril, o heteroaril o un anillo heterocíclico que comprende N, O y/o S; y

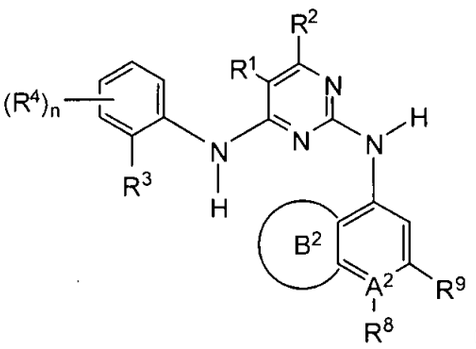
R^6 es isopropoxi o metoxi.

9. El compuesto de la Reivindicación 8, donde cada R^{11} es $(CR_2)_pCO_{1-2}R$, $(CR_2)_pOR$, $(CR_2)_pR^{13}$, $(CR_2)_pNRR^{12}$ o $(CR_2)_pCONRR^{12}$;

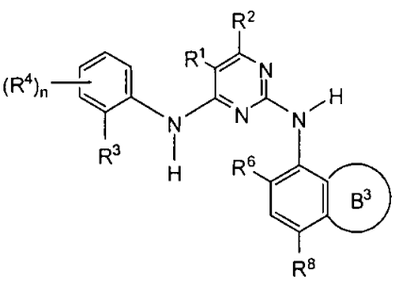
R y R^{12} son independientemente H o C_{1-6} alquil; y

R^{13} es un piperidinil, azetidiil, tetrahidropiranil, ciclohexil, morfolinil, pirrolidinil, heptametileneimina, octametileneimina, a unmina bicíclica o diamina derivative, quinuclidin-3-il, 8-metil-8-aza-biciclo[3.2.1]oct-6-il], o 9-metil-9-aza-biciclo[4.2.1]nonan-7-il, opcionalmente sustituidos.

10. El compuesto de la Reivindicación 1, donde dicho compuesto es de Fórmula (4A) o Fórmula (4B):



(4A)



(4B);

donde R^1 es halo o C_{1-6} alquil;

R^2 es H; o

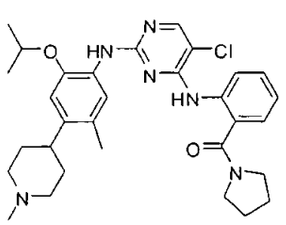
R^1 y R^2 juntos forman un anillo carbocíclico de 5-7 miembros opcionalmente sustituido, aril, o heteroaril o un anillo heterocíclico que comprende N, O y/o S;

R^6 es isopropoxi o metoxi; y

B^2 y B^3 son independientemente un aril o heteroaril de 5-6 miembros opcionalmente sustituido que contiene N, O o S.

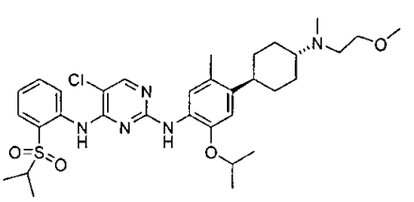
11. El compuesto de la Reivindicación 1, donde dicho compuesto se selecciona del grupo que consiste en

1



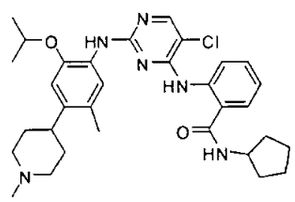
(2-(5-cloro-2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino) pirimidin-4-ilamino)fenil)(pirrolidin-1-il)metanona

124



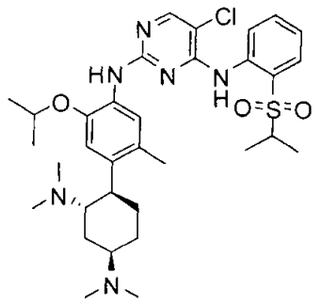
N2-(4-((1r,4r)-4-(N-(2-metoxietil)-N-metilamino)ciclohexil)-2-isopropoxi-5-metilfenil)-5-cloro-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina

2



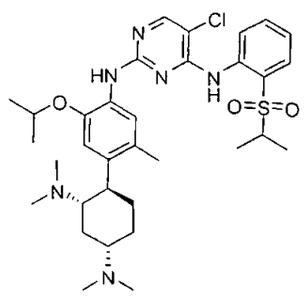
2-(5-cloro-2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino) pirimidin-4-ilamino)-N-ciclopentilbenzamida

3



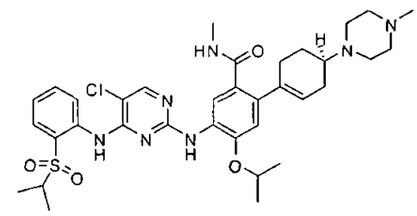
N2-(4-((1R,2S,4R)-2,4-bis(dimetilamino) ciclohexil)-2-isopropoxi-5-metilfenil)-5-cloro-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

4



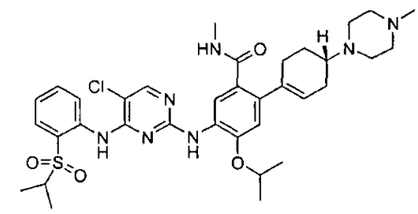
N2-(4-((1R,2S,4S)-2,4-bis(dimetilamino) ciclohexil)-2-isopropoxi-5-metilfenil)-5-cloro-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

125



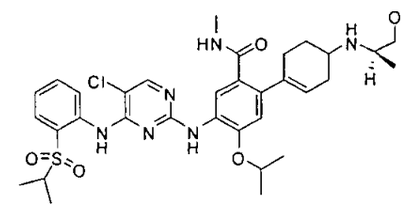
5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metil-2-((R)-4-(4-metilpiperazin-1-il)ciclohex-1-enil)benzamida

126



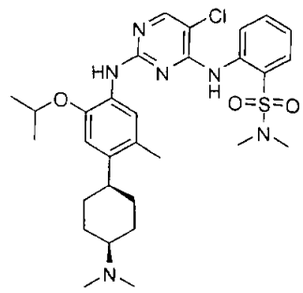
5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metil-2-((S)-4-(4-metilpiperazin-1-il)ciclohex-1-enil)benzamida

127



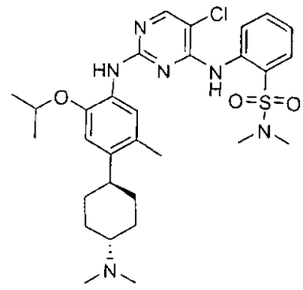
2-(4-((R)-1-hidroxipropan-2-ilamino)ciclohex-1-enil)-5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metilbenzamida

5



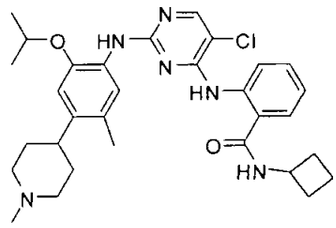
2-(5-cloro-2-(4-((1s,4s)-4-(dimetilamino) ciclohexil)-2-isopropoxi-5-metilfenilamino) pirimidin-4-ilamino)-N,Ndimetilbencenosulfonamida

6



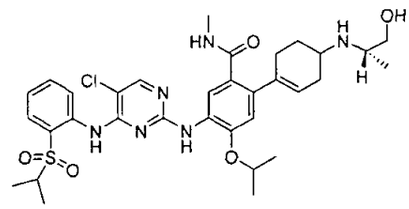
2-(5-cloro-2-(4-((1r,4r)-4-(dimetilamino)ciclohexil)-2-isopropoxi-5-metilfenilamino) pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida

7



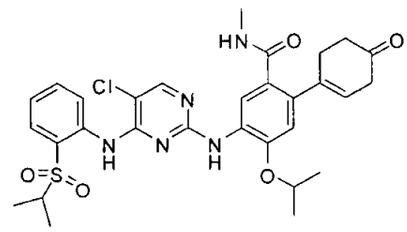
2-(5-cloro-2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino) pirimidin-4-ilamino)-N-ciclobutilbenzamida

128



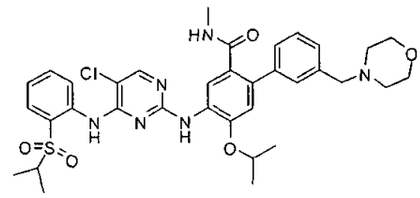
2-(4-((S)-1-hidroxipropan-2-ilamino)ciclohex-1-enil)-5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metilbenzamida

129



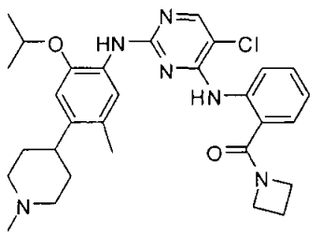
5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metil-2-(4-oxociclohex-1-enil)benzamida

130



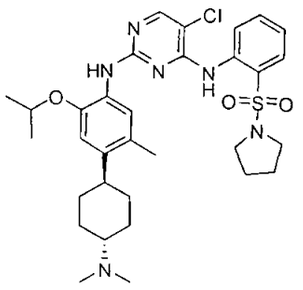
5-cloro-N4-(2-(isopropilsulfony)fenil)-N2-(2-isopropoxi-5-(N-metilcarboxamido)-4-(3-metil-4-(3-morfolinometil)-fenil)pirimidina-2,4-diamina

8



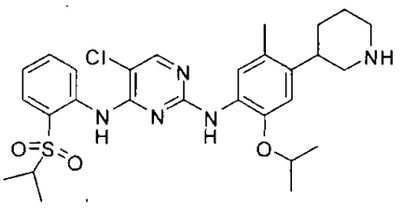
azetidin-1-il(2-(5-cloro-2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino) pirimidin-4-ilamino)fenil)metanona

9



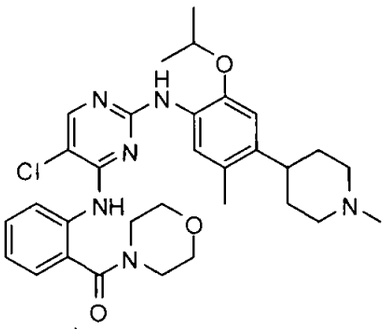
5-cloro-N2-(4-((1r,4r)-4-(dimetilamino) ciclohexil)-2-isopropoxi-5-metilfenil)-N4-(2-(pirrolidin-1-ilsulfonil)fenil) pirimidina-2,4-diamina

131



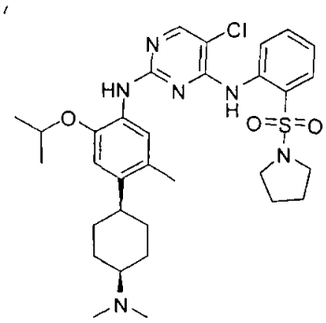
5-cloro-N2-(2-isopropoxi-5-metil-4-(piperidin-3-il)fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

132



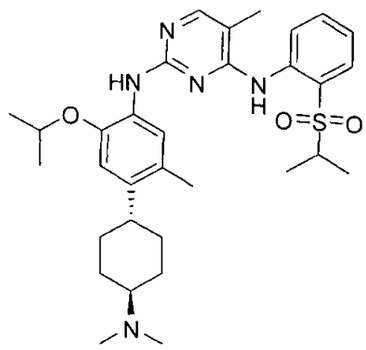
(2-(5-cloro-2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino)pirimidin-4-ilamino)fenil)(morfolino)metanona

10



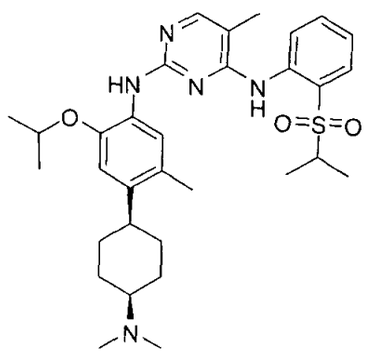
5-cloro-N2-(4-((1s,4s)-4-(dimetilamino) ciclohexil)-2-isopropoxi-5-metilfenil)-N4-(2-(pirrolidin-1-ilsulfonil)fenil) pirimidina-2,4-diamina

11



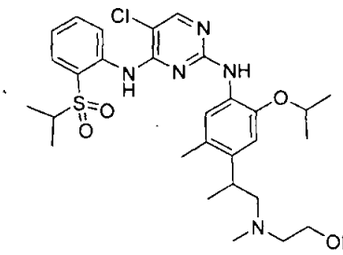
N2-(4-((1r,4r)-4-(dimetilamino)ciclohexil)-2-isopropoxi-5-metilfenil)-N4-(2-(isopropilsulfonil) fenil)-5-metilpirimidina-2,4-diamina

12



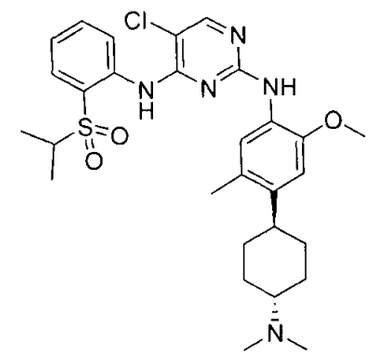
N2-(4-((1s,4s)-4-(dimetilamino) ciclohexil)-2-isopropoxi-5-metilfenil)-N4-(2-(isopropilsulfonil) fenil)-5-metilpirimidina-2,4-diamina

133



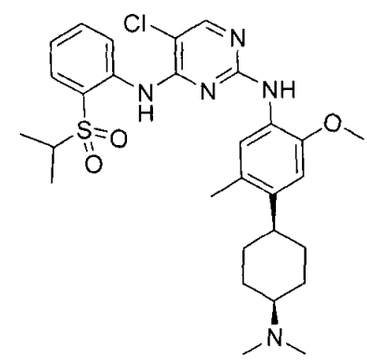
2-((2-(4-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) pirimidin-2-ilamino)-5-isopropoxi-2-metilfenil) propil)(metil)amino) etanol

134



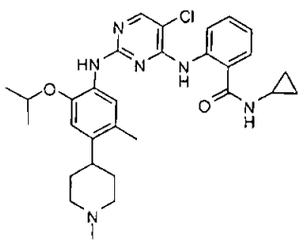
5-cloro-N2-(4-((1r,4r)-4-(dimetilamino) ciclohexil)-2-metoxi-5-metilfenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

135



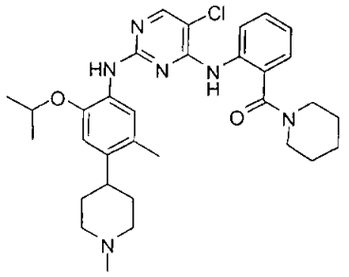
5-cloro-N2-(4-((1s,4s)-4-(dimetilamino) ciclohexil)-2-metoxi-5-metilfenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

13



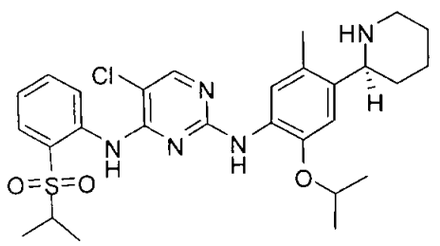
2-(5-cloro-2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino) pirimidin-4-ilamino)-N-ciclopropilbenzamida

14



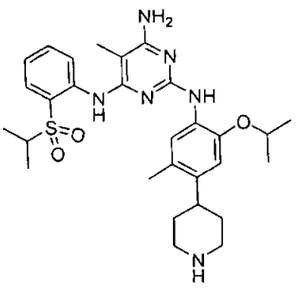
(2-(5-cloro-2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino) pirimidin-4-ilamino)fenil)(piperidin-1-il)metanona

15



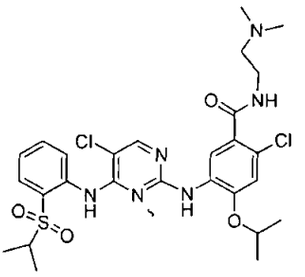
(S)-5-cloro-N2-(2-isopropoxi-5-metil-4-(piperidin-2-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina

136



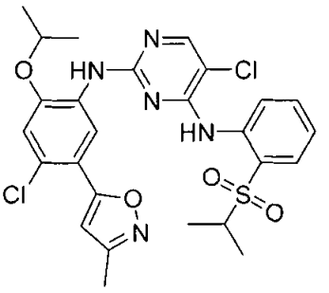
N2-(2-isopropoxi-5-metil-4-(piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil) fenil)-5-metilpirimidina-2,4,6-triamina

137



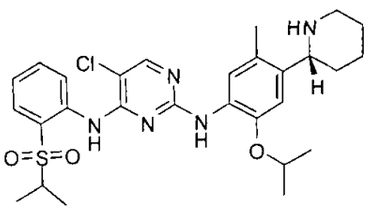
5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2-cloro-N-(2-(dimetilamino)etil)-4-isopropoxibenzamida

138



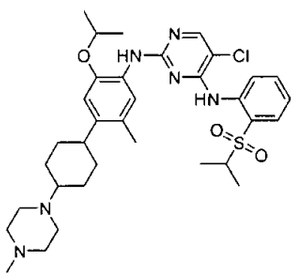
5-cloro-N2-(4-cloro-2-isopropoxi-5-(3-metilisoxazol-5-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina

16



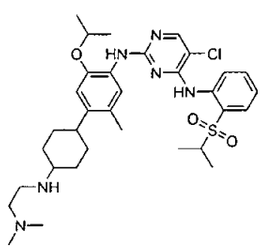
(R)-5-cloro-N2-(2-isopropoxi-5-metil-4-(piperidin-2-il)fenil)-N4-(2-(isopropilsulfonil)fenil) pirimidina-2,4-diamina

17



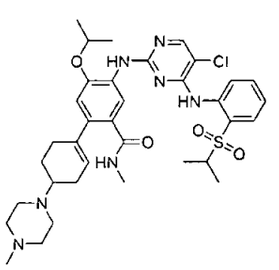
(*cis,trans*) 5-Cloro-N2-{2-isopropoxi-5-metil-4-[4-(4-metil-piperazin-1-il)-ciclohexil]-fenil}-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina

18

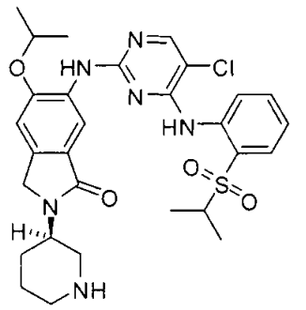


(*cis,trans*) 5-cloro-N2-{4-[4-(2-dimetilamino-etil amino)-ciclohexil]-2-isopropoxi-5-metil-fenil}-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina

19

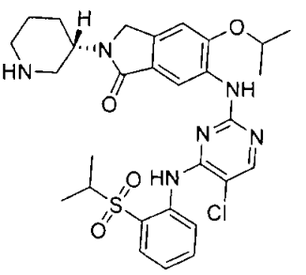


139



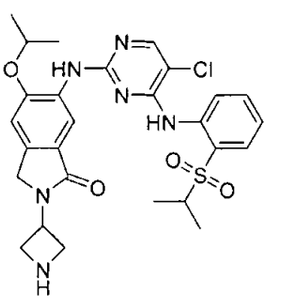
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-((R)-piperidin-3-il)isoindolin-1-ona

140



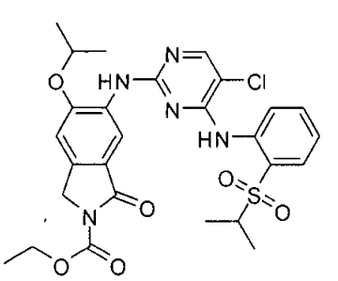
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-((S)-piperidin-3-il)isoindolin-1-ona

141



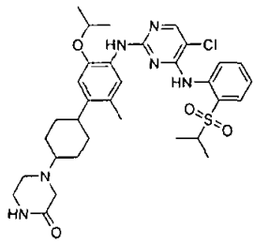
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2-(azetidin-3-il)-5-isopropoxiisoindolin-1-ona

142



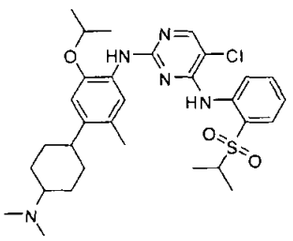
5-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-4-isopropoxi-N-metil-2-[4-(4-metil-piperazin-1-il)-ciclohex-1-enil]-benzamida

20



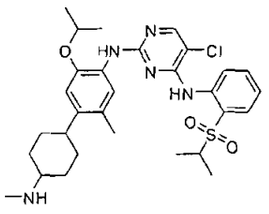
4-[4-(4-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-metil-fenil)-ciclohexil]-piperazin-2-ona

21



5-Cloro-N2-[4-(4-dimetilamino-ciclohexil)-2-isopropoxi-5-metil-fenil]-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina

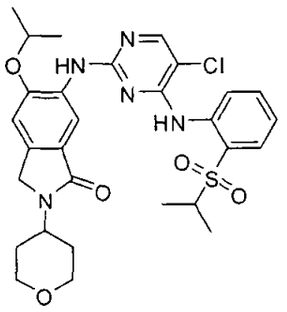
22



5-Cloro-N2-[2-isopropoxi-5-metil-4-(4-metilamino-ciclohexil)-fenil]-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina

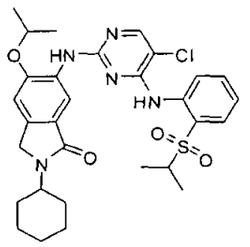
Etil 6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindoline-2-carboxilato

143



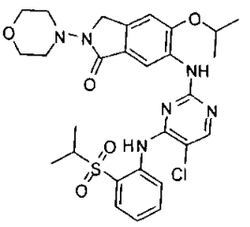
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2-(tetrahidro-2H-piran-4-il)-5-isopropoxiisoindolin-1-ona

144



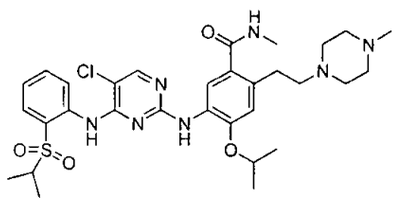
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloro pirimidin-2-ilamino)-2-ciclohexil-5-isopropoxi-isoindolin-1-ona

145



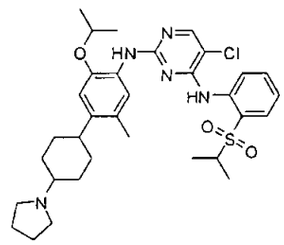
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloro pirimidin-2-ilamino)-5-isopropoxi-2-morfolino-isoindolin-1-ona

23



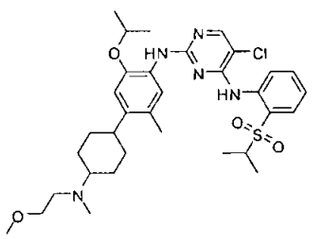
5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metil-2-(2-(4-metilpiperazin-1-il)etil)benzamida

24



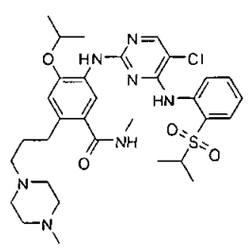
5-Cloro-N2-[2-isopropoxi-5-metil-4-(4-pirrolidin-1-il-ciclohexil)-fenil]-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina

25



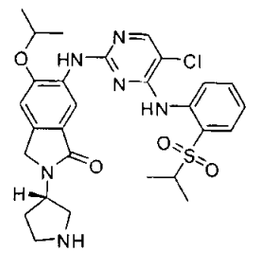
5-Cloro-N2-(2-isopropoxi-4-{4-[(2-metoxi-etil)-metil-amino]-ciclohexil}-5-metil-fenil)-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina

26



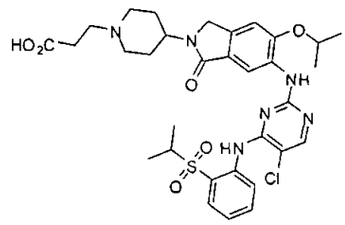
5-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-4-isopropoxi-N-metil-2-[3-(4-metil-piperazin-1-il)-propil]-benzamida

146



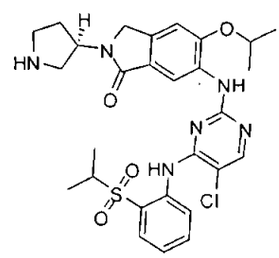
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-((S)-pirrolidin-3-il)isoindolin-1-ona

147



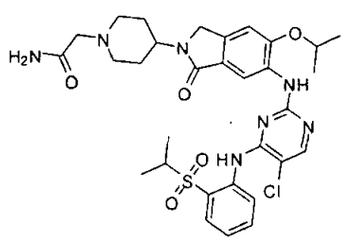
ácido 3-(4-(6-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)piperidin-1-il)propanoico

148



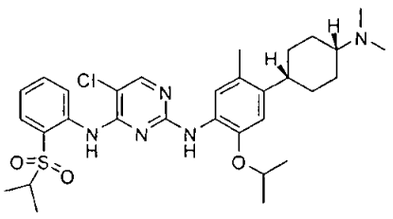
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-((R)-pirrolidin-3-il)isoindolin-1-ona

149



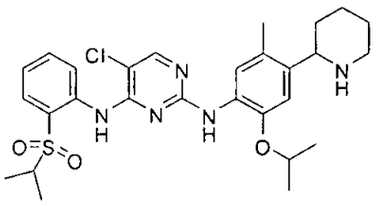
2-[4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenil-amino]-pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro-isoindol-2-il)-piperidin-1-il]-acetamida

27



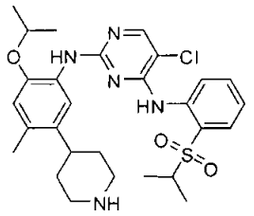
5-cloro-N2-(4-((1s,4s)-4-(dimetilamino) ciclohexil)-2-isopropoxi-5-metilfenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina

28



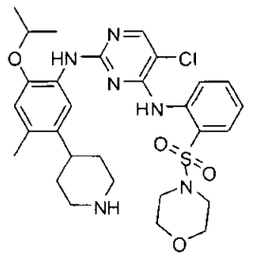
5-cloro-N2-(2-isopropoxi-5-metil-4-(piperidin-2-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina

29



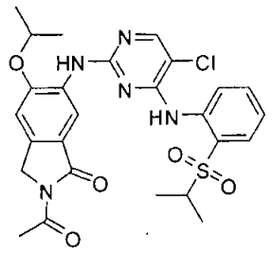
5-cloro-N2-(2-isopropoxi-4-metil-5-(piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil) pirimidina-2,4-diamina

30



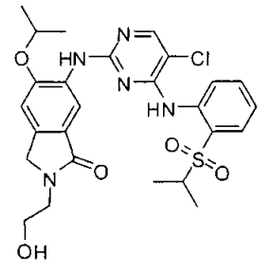
5-cloro-N2-(2-isopropoxi-4-metil-5-(piperidin-4-il)fenil)-N4-

150



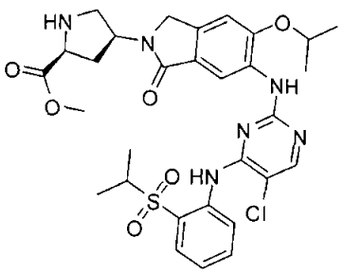
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2-acetil-5-isopropoxiisoindolin-1-ona

151



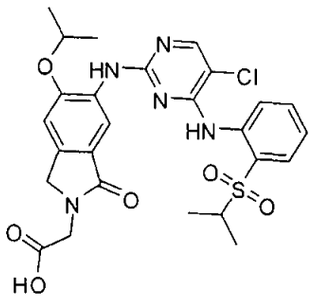
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2-(2-hidroxietil)-5-isopropoxiisoindolin-1-ona

152



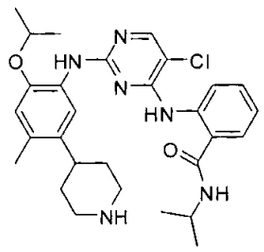
(2S,4S)-metil 4-(6-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)pirrolidina-2-carboxilato

153



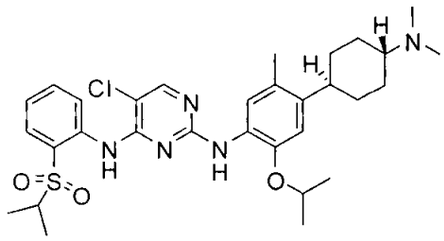
(2(morfolinosulfonamido) fenil)pirimidina-2,4-diamina

31



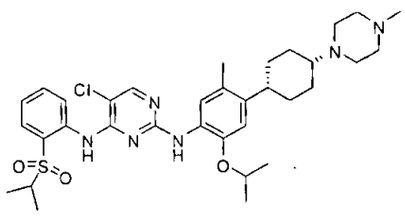
2-(2-(2-isopropoxi-4-metil-5-(piperidin-4-il)fenilamino)-5-cloropirimidin-4-ilamino)-N-isopropilbenzamida

32



5-cloro-N2-(4-((1r,4r)-4-(dimetilamino) ciclohexil)-2-isopropoxi-5-metilfenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina

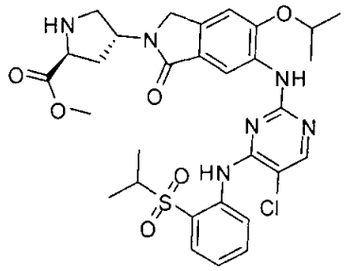
33



5-cloro-N2-(2-isopropoxi-5-metil-4-((1s,4s)-4-(4-metilpiperazin-1-il)ciclohexil)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina

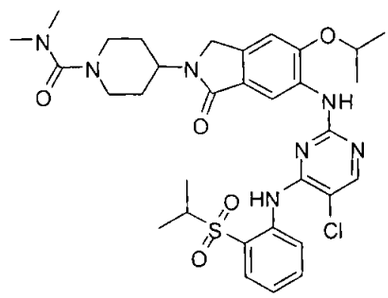
ácido 2-(6-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)acético

154



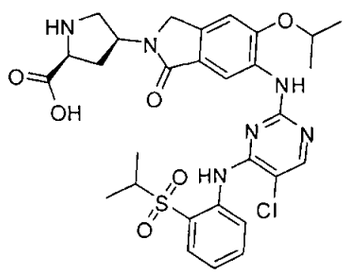
(2S,4R)-metil 4-(6-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)pirrolidina-2-carboxilato

155



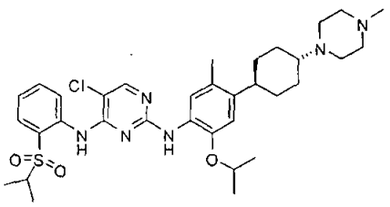
dimetilamida del ácido 4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro-isoindol-2-il)-piperidina-1-carboxílico

156



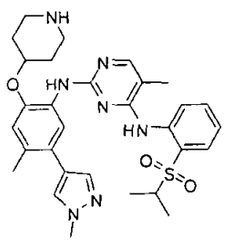
ácido (2S,4S)-4-(6-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)pirrolidina-2-carboxílico

34



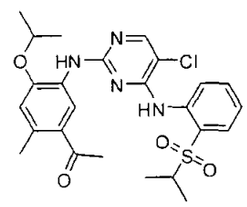
5-cloro-N2-(2-isopropoxi-5-metil-4-((1r,4r)-4-(4-metilpiperazin-1-il)ciclohexil)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina

35



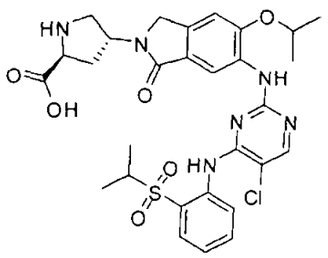
5-Metil-N2-[4-metil-5-(1-metil-1H-pirazol-4-il)-2-(piperidin-4-iloxi)-fenil]-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina

36



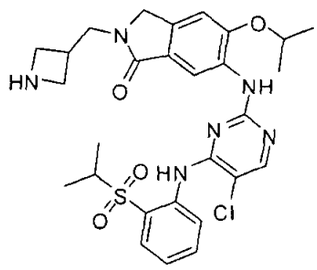
1-(5-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-4-isopropoxi-2-metil-fenil)-etanona

157



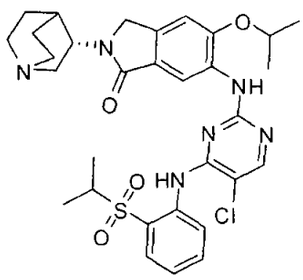
ácido (2S,4R)-4-(6-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)pirrolidina-2-carboxílico

158



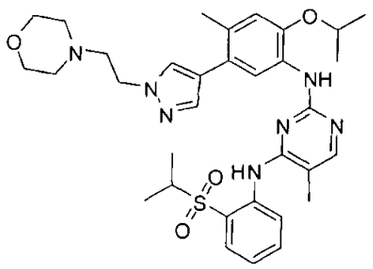
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2-((azetidin-3-il)metil)-5-isopropoxiisoindolin-1-ona

159



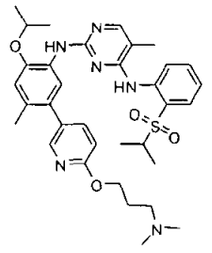
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-((S)-quinuclidin-3-il)isoindolin-1-ona

37



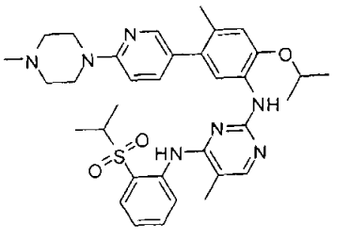
N2-{2-Isopropoxi-4-metil-5-[1-(2-morfolin-4-il-etil)-1H-pirazol-4-il]-fenil}-5-metil-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina

38



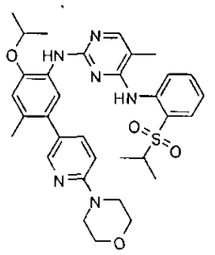
N2-(5-(6-(3-(dimetilamino)propoxi) piridin-3-il)-2-isopropoxi-4-metilfenil)-N4-(2-(isopropil sulfonil)fenil)-5-metilpirimidina-2,4-diamina

39

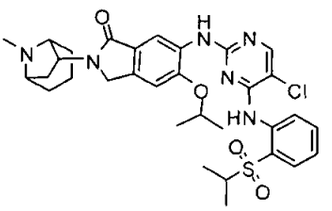


N2-(2-isopropoxi-4-metil-5-(6-(4-metilpiperazin-1-il)piridin-3-il)fenil)-N4-(2-(isopropilsulfonil) fenil)-5-metilpirimidina-2,4-diamina

40

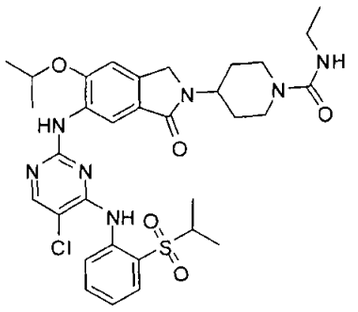


160



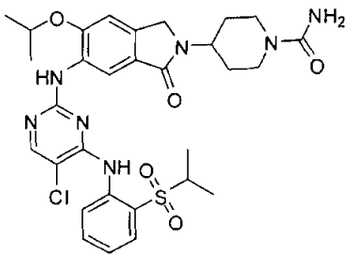
6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-(8-metil-8-aza-biciclo[3.2.1]oct-6-il)-2,3-dihidro-isoindol-1-ona

161



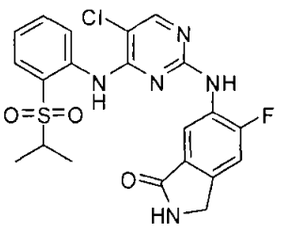
4-(6-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)-N-etilpiperidina-1-carboxamida

162



4-(6-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)piperidina-1-carboxamida

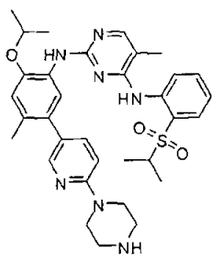
163



6-(4-(2-(isopropilsulfonil)fenilamino)-5-

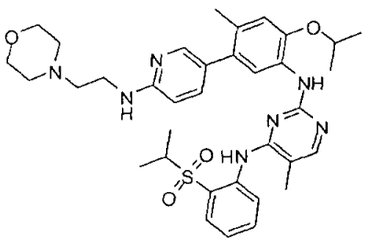
N2-(2-isopropoxi-4-metil-5-(6-morfolinopiridin-3-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-5-metilpirimidina-2,4-diamina

41



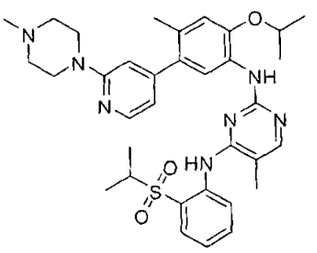
N2-(2-isopropoxi-4-metil-5-(6-(piperazin-1-il)piridin-3-il)fenil)-N4-(2-(isopropilsulfonil) fenil)-5-metilpirimidina-2,4-diamina

42



N2-(5-(6-(2-morfolinoetilamino) piridin-3-il)-2-isopropoxi-4-metilfenil)-N4-(2-(isopropil-sulfonil)fenil)-5-metilpirimidina-2,4-diamina

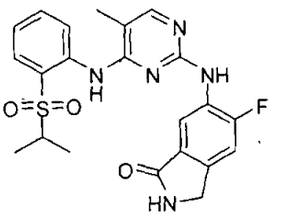
43



N2-(2-isopropoxi-4-metil-5-(2-(4-metilpiperazin-1-il)piridin-4-il)fenil)-N4-(2-(isopropilsulfonil) fenil)-5-metilpirimidina-2,4-diamina

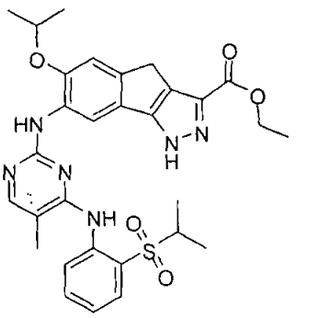
cloropirimidin-2-ilamino)-5-fluoroisoindolin-1-ona

164



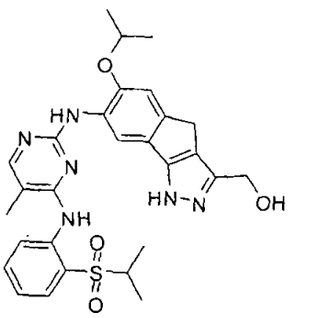
6-(4-(2-(isopropilsulfonil)fenilamino)-5-metilpirimidin-2-ilamino)-5-fluoroisoindolin-1-ona

165



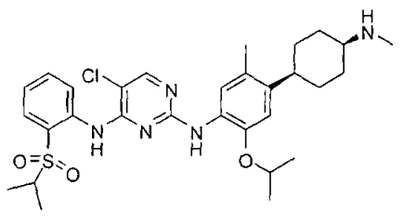
Etil 7-(4-(2-(isopropilsulfonil) fenilamino)-5-metilpirimidin-2-ilamino)-1,4-dihidro-6-isopropoxiindeno[1,2-c]pirazol-3-carboxilato

166



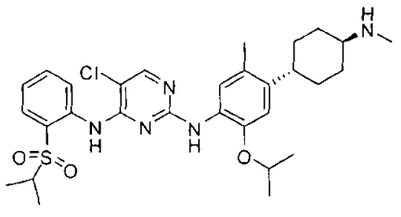
(7-(4-(2-(isopropilsulfonil)fenilamino)-5-metilpirimidin-2-ilamino)-1,4-dihidro-6-isopropoxiindeno[1,2-c]pirazol-3-il)metanol

44



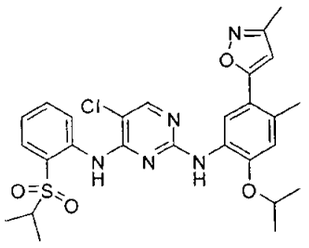
5-cloro-N2-(2-isopropoxi-5-metil-4-((1s,4s)-4-(metilamino)ciclohexil) fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

45



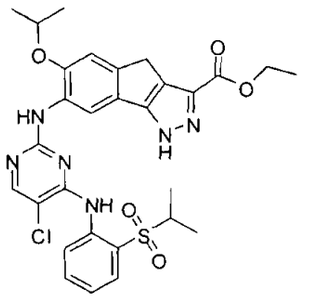
5-cloro-N2-(2-isopropoxi-5-metil-4-((1r,4r)-4-(metilamino)ciclohexil) fenil)-N4-(2-(isopropilsulfonil)fenil) pirimidina-2,4-diamina

46



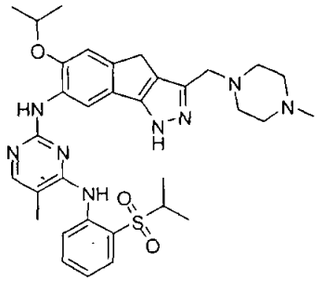
5-cloro-N2-(2-isopropoxi-4-metil-5-(3-metilisoxazol-5-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina

167



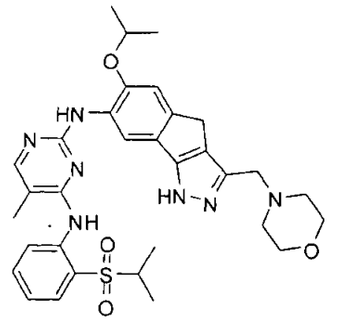
Etil 7-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-1,4-dihidro-6-isopropoxiindeno[1,2-c]pirazol-3-carboxilato

168



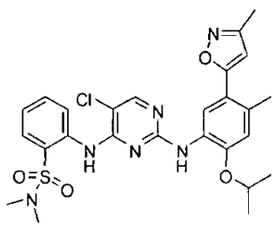
N2-(1,4-dihidro-6-isopropoxi-3-((4-metilpiperazin-1-il)metil)indeno[1,2-c]pirazol-7-il)-N4-(2-(isopropilsulfonil)fenil)-5-metilpirimidina-2,4-diamina

169



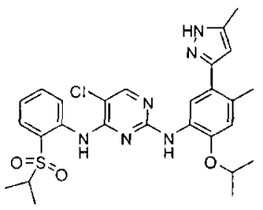
N2-(1,4-dihidro-6-isopropoxi-3-(morfolinometil) indeno[1,2-c]pirazol-7-il)-N4-(2-(isopropilsulfonil) fenil)-5-metilpirimidina-2,4-diamina

47



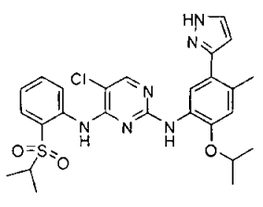
2-(5-cloro-2-(2-isopropoxi-4-metil-5-(3-metilisoxazol-5-il)fenilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida

48



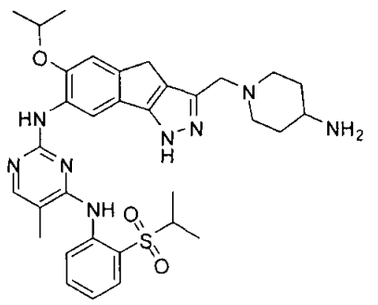
5-cloro-N2-(2-isopropoxi-4-metil-5-(5-metil-1H-pirazol-3-il)fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

49



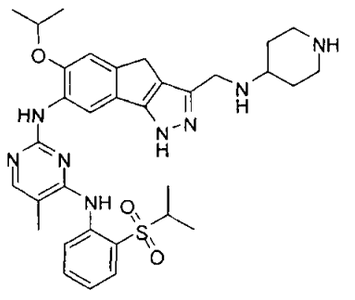
5-cloro-N2-(2-isopropoxi-4-metil-5-(1H-pirazol-3-il)fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

170



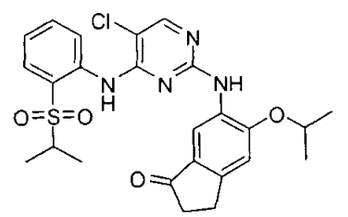
N2-(3-((4-aminopiperidin-1-il)metil)-1,4-dihidro-6-isopropoxiindeno[1,2-c]pirazol-7-il)-N4-(2-(isopropilsulfonil)fenil)-5-metilpirimidina-2,4-diamina

171



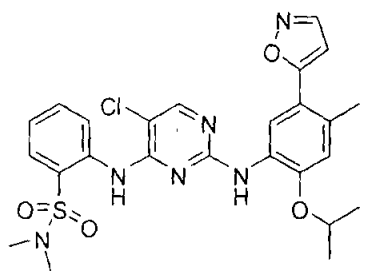
N2-(1,4-dihidro-6-isopropoxi-3-((piperidin-4-ilamino)metil)indeno[1,2-c]pirazol-7-il)-N4-(2-(isopropilsulfonil)fenil)-5-metilpirimidina-2,4-diamina

172



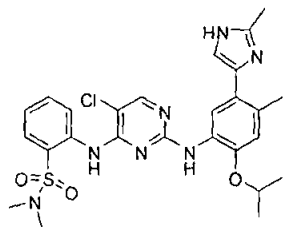
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2,3-dihidro-5-isopropoxiinden-1-ona

50



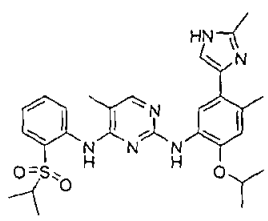
2-(5-cloro-2-(2-isopropoxi-5-(isoxazol-5-il)-4-metilfenilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida

51



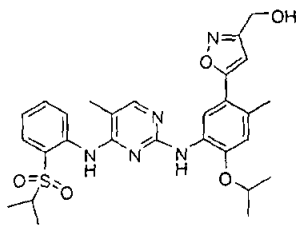
2-(5-cloro-2-(2-isopropoxi-4-metil-5-(2-metil-1H-imidazol-4-il) fenilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida

52



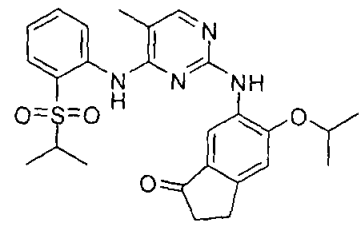
5-cloro-N2-(2-isopropoxi-4-metil-5-(2-metil-1H-imidazol-4-il)fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

53



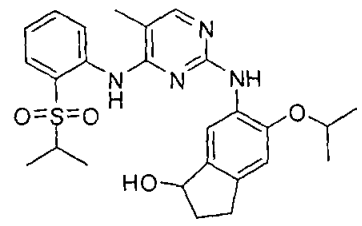
(5-(5-(4-(2-(isopropilsulfonil) fenilamino)-5-metilpirimidin-2-ilamino)-4-isopropoxi-2-

173



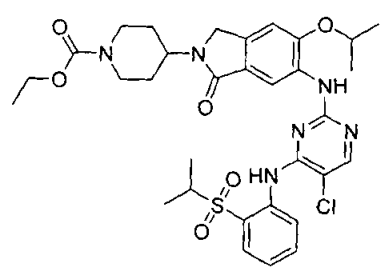
6-(4-(2-(isopropilsulfonil)fenilamino)-5-metilpirimidin-2-ilamino)-2,3-dihidro-5-isopropoxiinden-1-ona

174



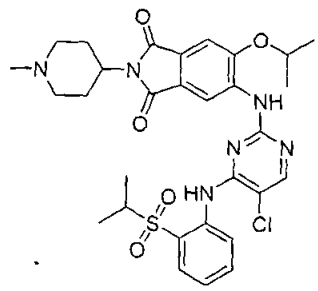
6-(4-(2-(isopropilsulfonil)fenilamino)-5-metil pirimidin-2-ilamino)-2,3-dihidro-5-isopropoxi-1H-inden-1-ol

175



éster etílico del ácido 4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino] -pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro -isoindol-2-il)-piperidina-1-carboxílico

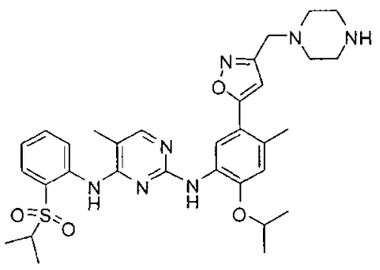
176



5-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-6-

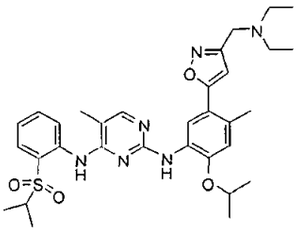
metilfenil)isoxazol-3-il)metanol

54



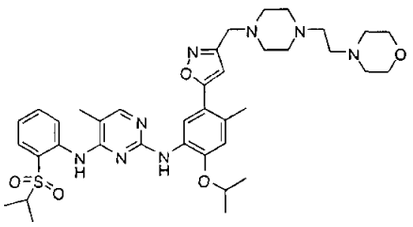
N2-(2-isopropoxi-4-metil-5-(3-((piperazin-1-il)metil)isoxazol-5-il)fenil)-N4-(2-(isopropil-sulfonil)fenil)-5-metilpirimidina-2,4-diamina

55



N2-(5-(3-((dietilamino)metil) isoxazol-5-il)-2-isopropoxi-4-metilfenil)-N4-(2-(isopropil-sulfonil)fenil)-5-metilpirimidina-2,4-diamina

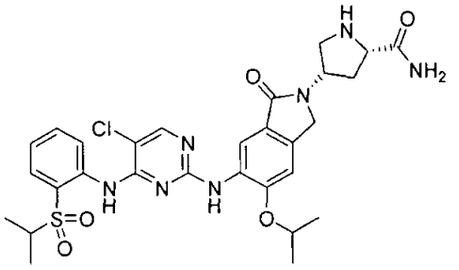
56



N2-(2-isopropoxi-4-metil-5-(3-((4-(2-morfolinoetil)piperazin-1-il)metil)isoxazol-5-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-5-metilpirimidina-2,4-diamina

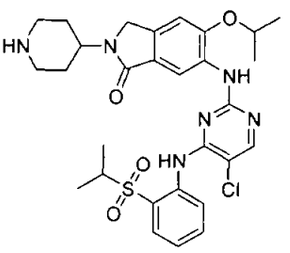
isopropoxi-2-(1-metil-piperidin-4-il)-isoindol-1,3-diona

177



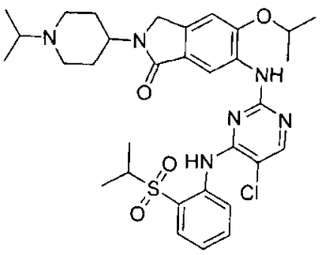
amida del ácido (2S, 4S)-4-(6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-1-oxo-1,3-dihidro-isoindol-2-il)-pirrolidina-2-carboxílico

178



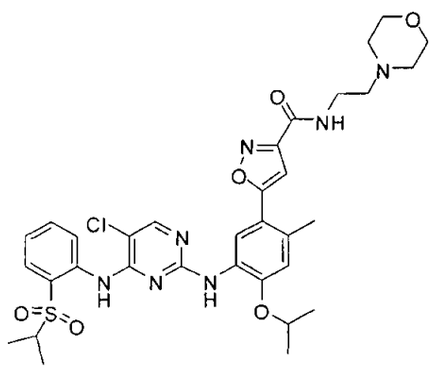
6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-piperidin-4-il-2,3-dihidro-isoindol-1-ona

179



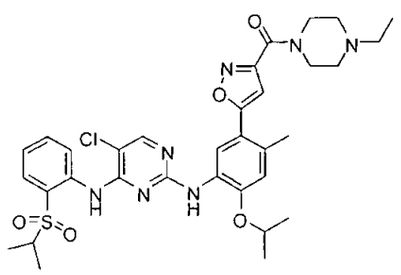
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-(1-isopropilpiperidin-4-il)isoindolin-1-ona

57



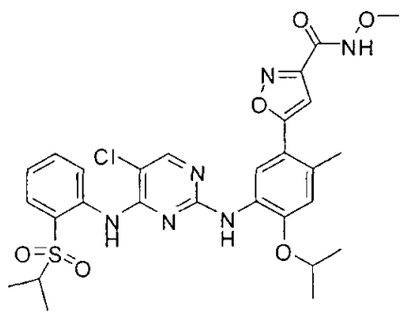
5-(5-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-2-metilfenil)-N-(2-morfolinoetil)isoxazol-3-carboxamida

58



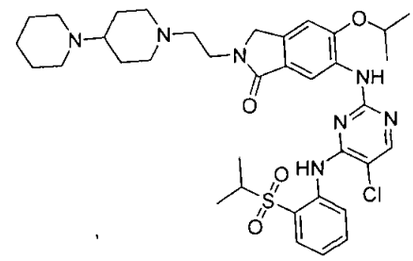
(5-(5-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-2-metilfenil)isoxazol-3-il)(4-etilpiperazin-1-il)metanona

59



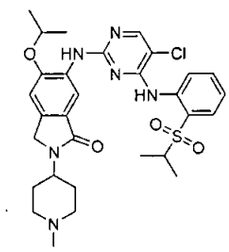
5-(5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-2-metilfenil)-N-metoxiisoxazol-3-carboxamida

180



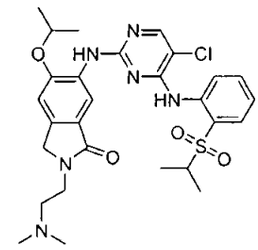
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-(2-(4-(piperidin-1-il)piperidin-1-il)etil)isoindolin-1-ona

181



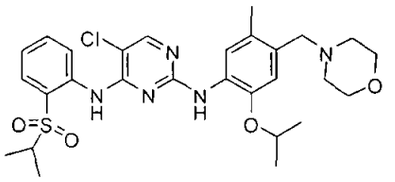
6-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-(1-metil-piperidin-4-il)-2,3-dihidro-isoindol-1-ona

182



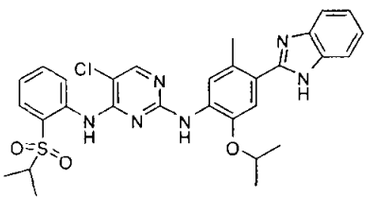
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloro pirimidin-2-ilamino)-2-(1-(2-(dimetilamino)etil) piperidin-4-il)-5-isopropoxiisoindolin-1-ona

60



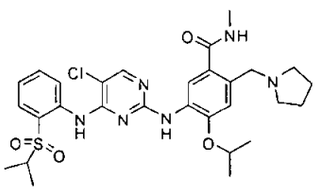
5-Cloro-N2-(2-isopropoxi-5-metil-4-morfolin-4-ilmetil-fenil)-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina

61



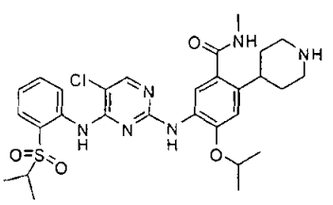
N2-(4-(1H-benzo[d]imidazol-2-il)-2-isopropoxi-5-metilfenil)-5-cloro-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

62



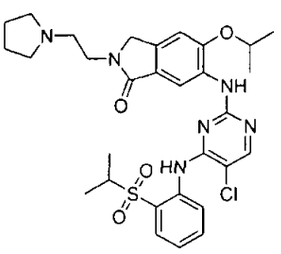
5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metil-2-((pirrolidin-1-il)metil)benzamida

63



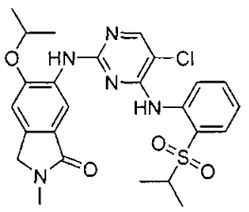
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183



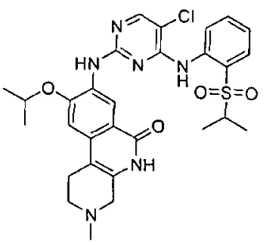
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-(1-(2-(pirrolidin-1-il)etil)piperidin-4-il)isoindolin-1-ona

184



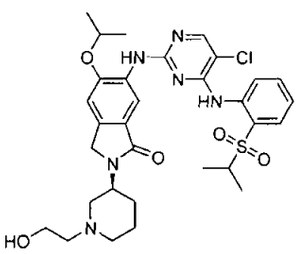
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-metilisoindolin-1-ona

185



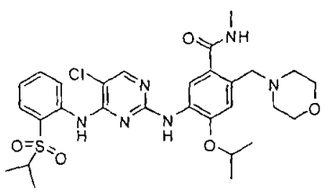
8-(5-cloro-4-(2-(isopropilsulfonil) fenilamino) pirimidin-2-ilamino)-9-isopropoxi-3-metil-1,2,3,4-tetrahidrobenzo[c][1,7]naftiridin-6(5H)-ona

186



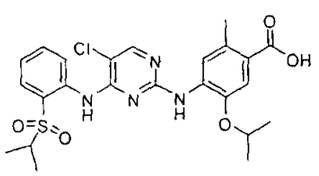
(S)-6-(5-cloro-4-(2-(isopropilsulfonil) fenilamino) pirimidin-2-ilamino)-2-(1-(2-hidroxietil)piperidin-3-il)-5-

64



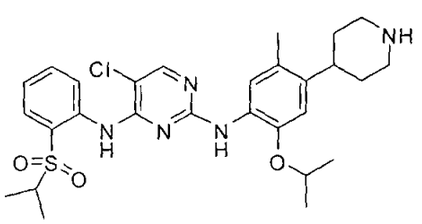
5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metil-2-(morfolinometil)benzamida

65



ácido 4-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-metilbenzóico

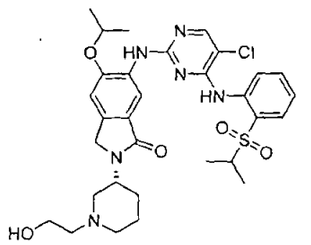
66



5-cloro-N2-(2-isopropoxi-5-metil-4-(piperidin-4-il)fenil)-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina

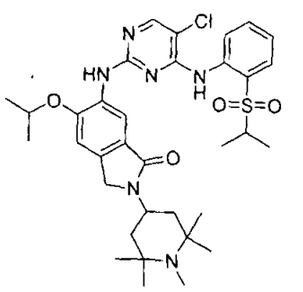
isopropoxiisoindolin-1-ona

187



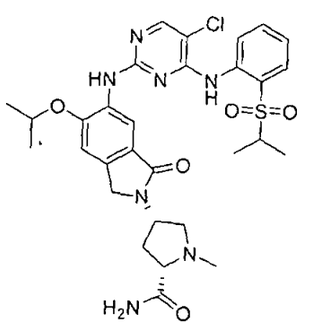
(R)-6-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) pirimidin-2-ilamino)-2-(1-(2-hidroxietil)piperidin-3-il)-5-isopropoxiisoindolin-1-ona

188



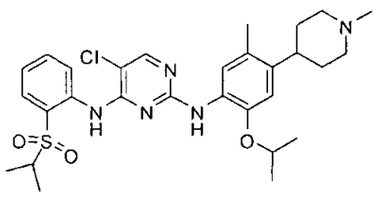
6-(5-cloro-4-(2-(isopropilsulfonil) fenilamino) pirimidin-2-ilamino)-5-isopropoxi-2-(1,2,2,6,6-pentametil piperidin-4-il)isoindolin-1-ona

189



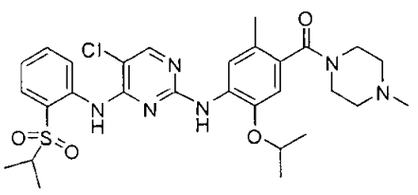
(2S,4S)-4-(6-(5-cloro-4-(2-(isopropilsulfonil) fenilamino) pirimidin-2-ilamino)-5-isopropoxi-1-oxoisoindolin-2-il)-1-metilpirrolidina-2-carboxamida

67



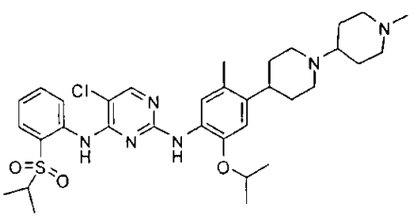
5-cloro-N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-[2-(propano-2-sulfonil)fenil]-pirimidina-2,4-diamina

68



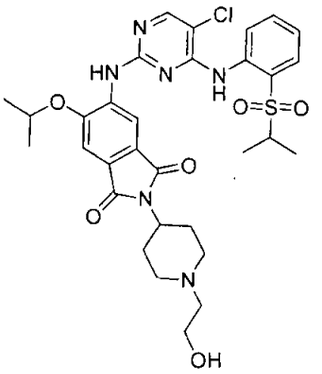
(4-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-metilfenil)(4-metilpiperazin-1-il)metanona

69



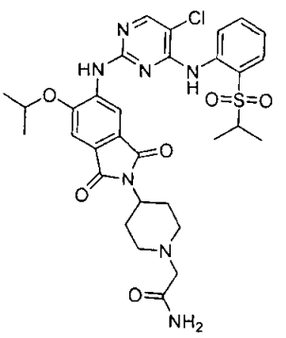
5-cloro-N2-(2-isopropoxi-5-metil-4-(1-(1-metilpiperidin-4-il)piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

190



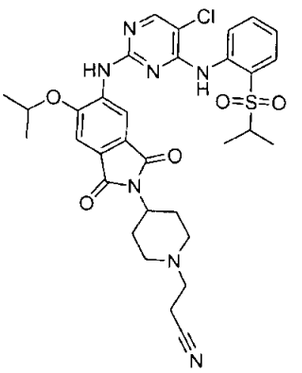
5-(5-cloro-4-(2-(isopropilsulfonil) fenilamino) pirimidin-2-ilamino)-2-(1-(2-hidroxietil)piperidin-4-il)-6-isopropoxiisoindoline-1,3-diona

191



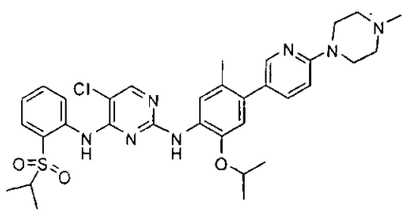
2-(4-(5-(5-cloro-4-(2-(isopropilsulfonil) fenilamino) pirimidin-2-ilamino)-6-isopropoxi-1,3-dioxoisoindolin-2-il)piperidin-1-il)acetamida

192



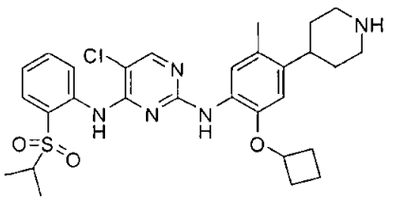
3-(4-(5-(5-cloro-4-(2-(isopropilsulfonil) fenilamino)pirimidin-2-ilamino)-6-isopropoxi-1,3-dioxoisoindolin-2-il)piperidin-1-il)propanonitrilo

70



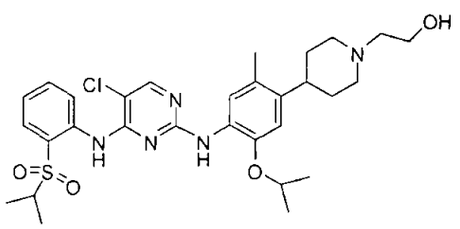
5-cloro-N2-(2-isopropoxi-5-metil-4-(6-(4-metilpiperazin-1-il)piridin-3-il)fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

71



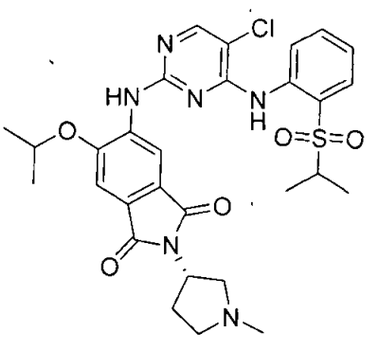
5-cloro-N2-(2-ciclobutoxi-5-metil-4-(piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina

72



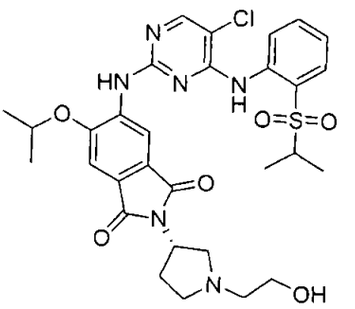
2-[4-(4-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-5-isopropoxi-2-metil-fenil)-piperidin-1-il]-etanol

193



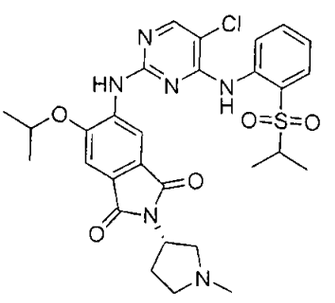
(S)-5-(5-cloro-4-(2-(isopropilsulfonil) fenilamino) pirimidin-2-ilamino)-6-isopropoxi-2-(1-metilpirrolidin-3-il)isoindoline-1,3-diona

194



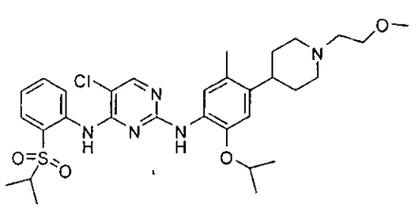
(S)-5-(5-cloro-4-(2-(isopropilsulfonil) fenilamino) pirimidin-2-ilamino)-2-(1-(2-hidroxietil)pirrolidin-3-il)-6-isopropoxiisoindoline-1,3-diona

195



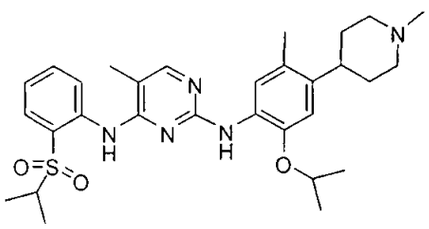
(S)-5-(5-cloro-4-(2-(isopropilsulfonil) fenilamino) pirimidin-2-ilamino)-6-isopropoxi-2-(1-metilpirrolidin-3-il)isoindoline-1,3-diona

73



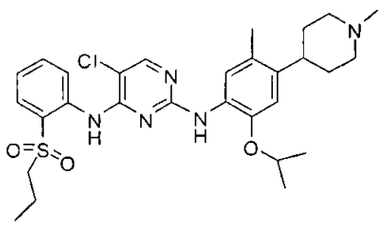
5-cloro-N2-(2-isopropoxi-4-(1-(2-metoxietil)piperidin-4-il)-5-metilfenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

74



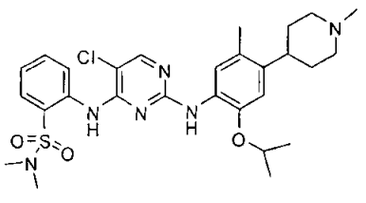
N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-5-metilpirimidina-2,4-diamina

75



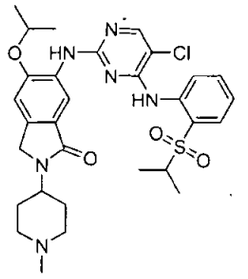
5-cloro-N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(propilsulfonil)fenil)pirimidina-2,4-diamina

76



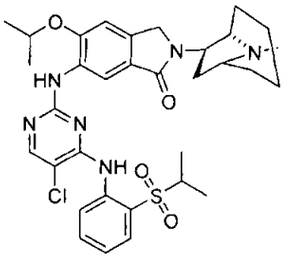
2-(5-cloro-2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino) pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida

196



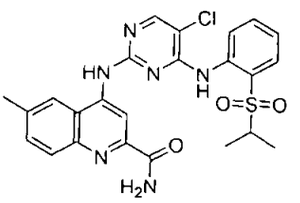
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-(1-metilpiperidin-4-il)isoindolin-1-ona

197



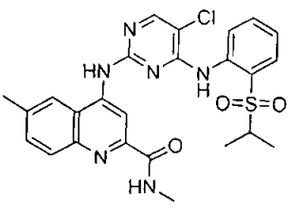
6-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-((6S,7R)-9-metil-9-aza-biciclo[4.2.1]nonan-7-il)isoindolin-1-ona

198



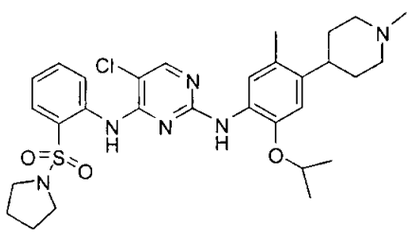
amida del ácido 4-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-6-metil-quinolina-2-carboxílico

199



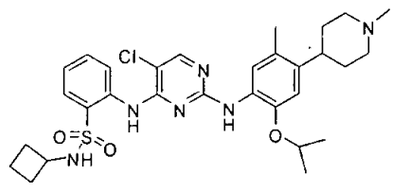
metilamida del ácido 4-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-6-metil-quinolina-2-carboxílico

77



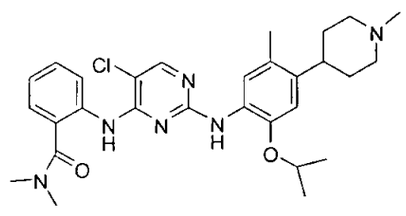
5-cloro-N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(pirrolidin-1-ilsulfonil)fenil) pirimidina-2,4-diamina

78



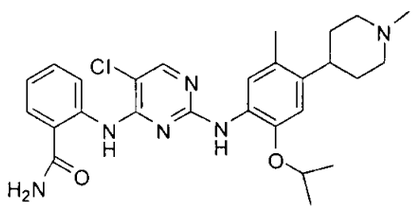
5-cloro-N4-(2-(ciclobutilaminosulfonil)fenil)-N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)pirimidina-2,4-diamina

79



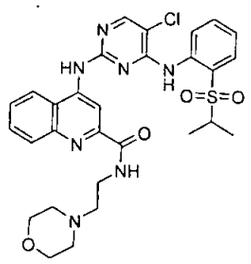
2-(2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino)-5-cloropirimidin-4-ilamino)-N,N-dimetilbenzamida

80



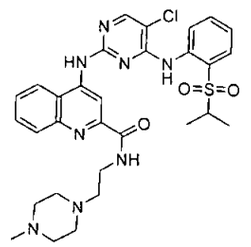
2-(2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenilamino)-5-cloropirimidin-4-ilamino) benzamida

200



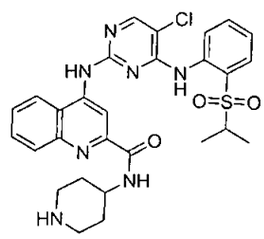
4-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-quinolina-2-carboxílico ácido (2-morfolin-4-il-etil)-amida

201



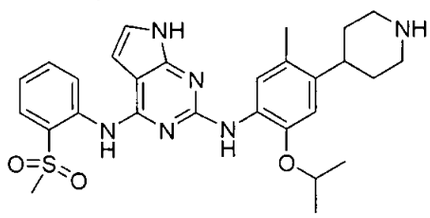
4-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-quinolina-2-carboxílico ácido [2-(4-metil-piperazin-1-il)-etil]-amida

202



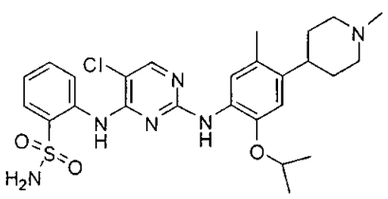
4-{5-Cloro-4-[2-(propano-2-sulfonil)-fenilamino]-pirimidin-2-ilamino}-quinolina-2-carboxílico ácido piperidin-4-ilamida

203



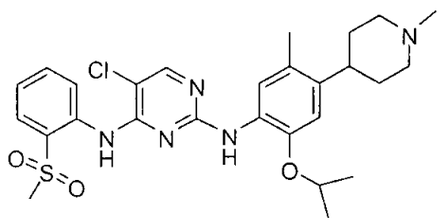
N2-(2-isopropoxi-5-metil-4-(piperidin-4-il)fenil)-N4-(2-(metilsulfonil)fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina

81



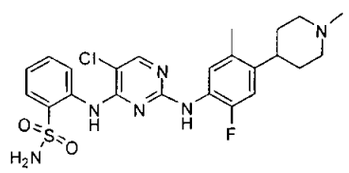
5-cloro-N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(aminosulfonil)fenil)pirimidina-2,4-diamina

82



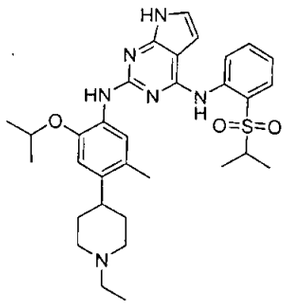
5-cloro-N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(metilsulfonil)fenil)pirimidina-2,4-diamina

83



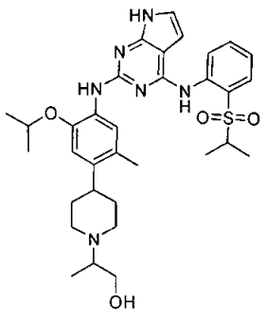
5-cloro-N2-(2-fluoro-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(aminosulfonil)fenil)pirimidina-2,4-diamina

204



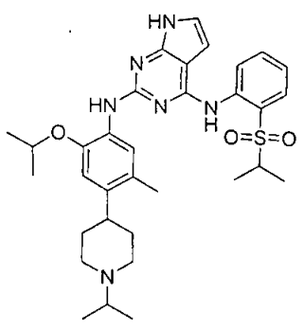
N2-(4-(1-etilpiperidin-4-il)-2-isopropoxi-5-metilfenil)-N4-(2-(isopropilsulfonil)fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina

205



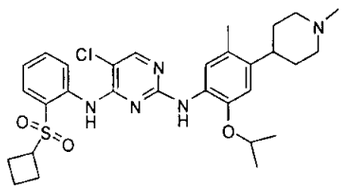
2-(4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)piperidin-1-il)propan-1-ol

206



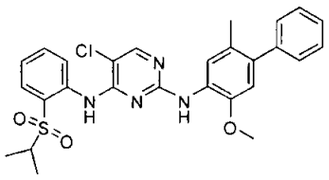
N2-(2-isopropoxi-4-(1-isopropilpiperidin-4-il)-5-metilfenil)-N4-(2-(isopropilsulfonil)fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina

84



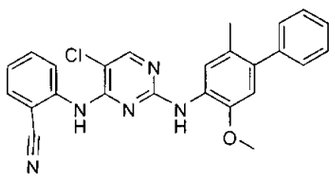
5-cloro-N4-(2-(ciclobutilsulfonil)fenil)-N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)pirimidina-2,4-diamina

85



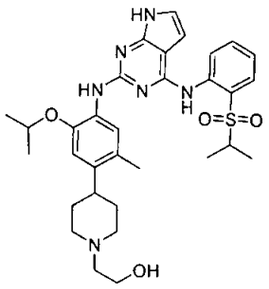
5-cloro-N4-(2-(isopropilsulfonil) fenil)-N2-(2-metoxi-5-metil-4-fenil)-fenil)pirimidina-2,4-diamina

86



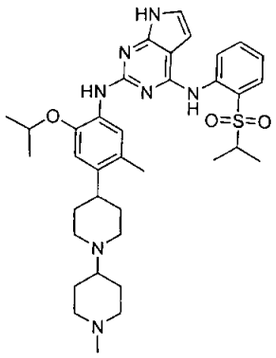
5-cloro-N4-(2-cianofenil)-N2-(2-metoxi-5-metil-4-fenil)-fenil)pirimidina-2,4-diamina

207



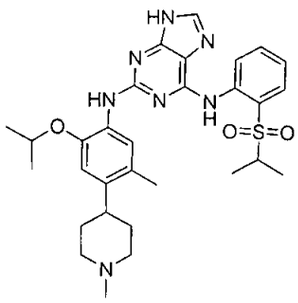
2-(4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)piperidin-1-il)etanol

208



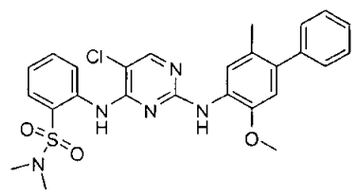
N2-(2-isopropoxi-5-metil-4-(1'-metil-1,4'-bipiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil) fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina

209



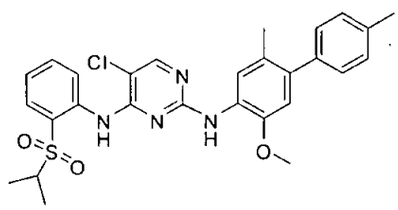
N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N6-(2-(isopropilsulfonil)fenil)-9H-purina-2,6-diamina

87



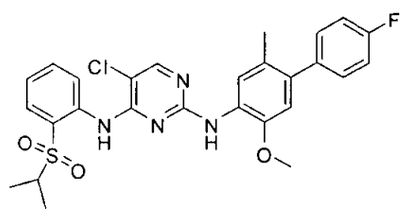
2-(5-cloro-2-(5-metoxi-2-metilbifenil-4-ilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida

88



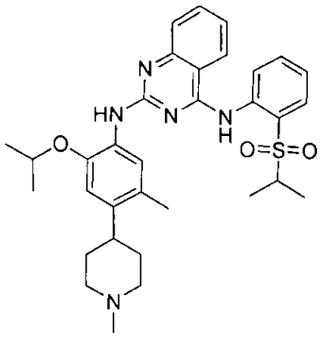
5-cloro-N4-(2-(isopropilsulfonil) fenil)-N2-(2-metoxi-5-metil-4-(4-metilfenil)-fenil)pirimidina-2,4-diamina

89



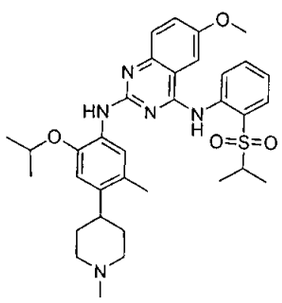
5-cloro-N4-(2-(isopropilsulfonil) fenil)-N2-(2-metoxi-5-metil-4-(4-fluorofenil)-fenil)pirimidina-2,4-diamina

210



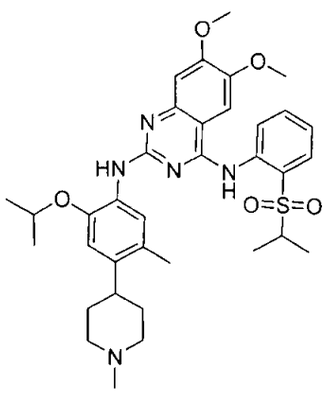
N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)quinazolina-2,4-diamina

211



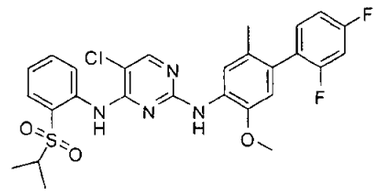
N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-6-metoxiquinazolina-2,4-diamina

212



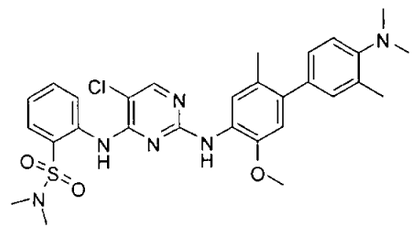
N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-6,7-dimetoxiquinazolina-2,4-diamina

90



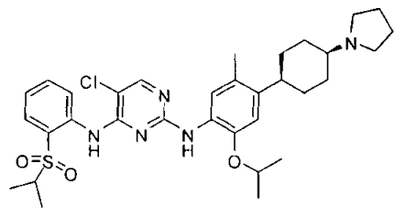
5-cloro-N4-(2-(isopropilsulfonil) fenil)-N2-(2-metoxi-5-metil-4-(2,4-difluorofenil)-fenil)pirimidina-2,4-diamina

91



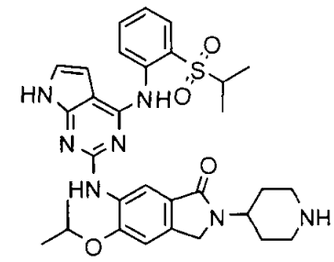
2-(5-cloro-2-(4'-(dimetilamino)-5-metoxi-2,3'-dimetilbifenil-4-ilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida

92



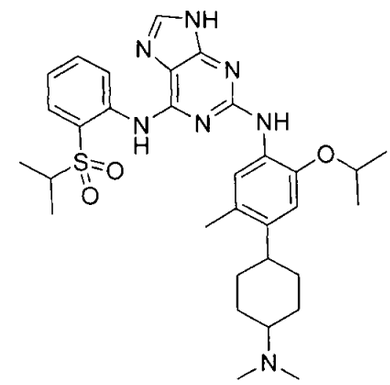
5-cloro-N2-(2-isopropoxi-5-metil-4-((1s,4s)-4-(pirrolidin-1-il)ciclohexil)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina

213



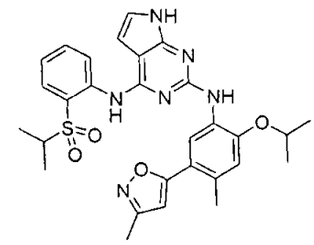
5-isopropoxi-6-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-(piperidin-4-il)isoindolin-1-ona

214



N2-(4-(4-(dimetilamino)ciclohexil)-2-isopropoxi-5-metilfenil)-N6-(2-(isopropilsulfonil)fenil)-9H-purina-2,6-diamina

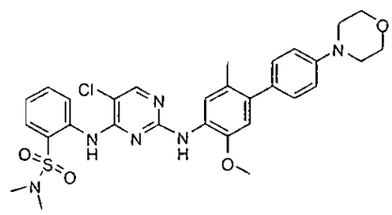
215



N2-(2-isopropoxi-4-metil-5-(3-metilisoxazol-5-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina

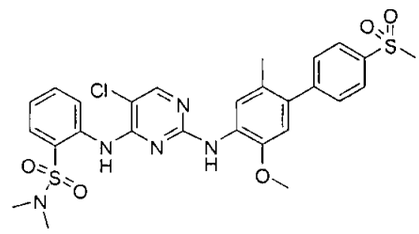
382

93



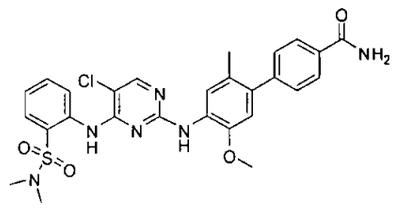
2-(5-cloro-2-(5-metoxi-2-metil-4'-morfolinobifenil-4-ilamino) pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida

94



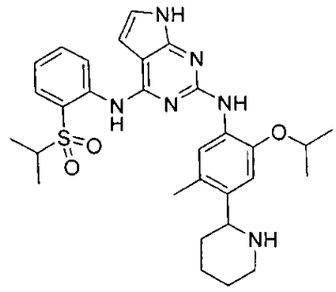
2-(5-cloro-2-(5-metoxi-2-metil-4'-(metilsulfonil)bifenil-4-ilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida

95



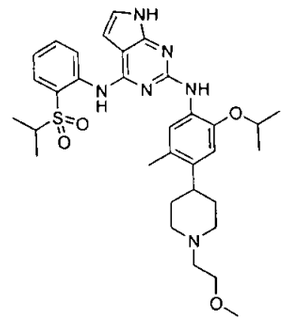
4'-(5-cloro-4-(2-(N,N-dimetilsulfamoil) fenilamino) pirimidin-2-ilamino)-5'-metoxi-2'-metilbifenil-4-carboxamida

216



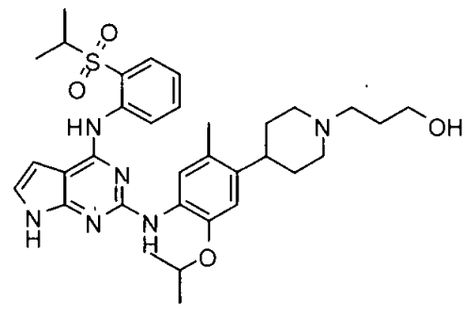
N2-(2-isopropoxi-5-metil-4-(piperidin-2-il)fenil)-N4-(2-(isopropilsulfonil) fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina

217



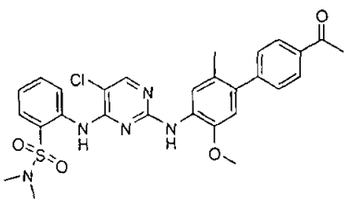
N2-(2-isopropoxi-4-(1-(2-metoxietil)piperidin-4-il)-5-metilfenil)-N4-(2-(isopropilsulfonil) fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina

218



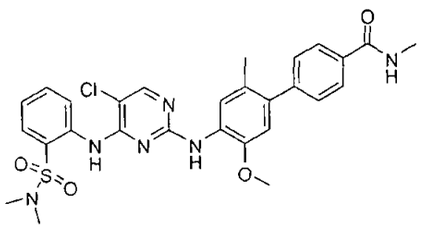
3-(4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)piperidin-1-il)propan-1-ol

96



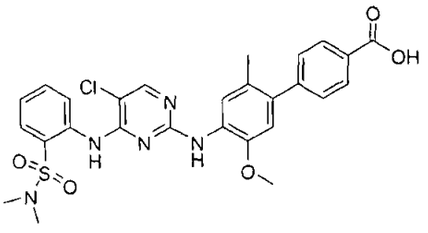
2-(2-(4'-acetil-5-metoxi-2-metilbifenil-4-ilamino)-5-cloropirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida

97



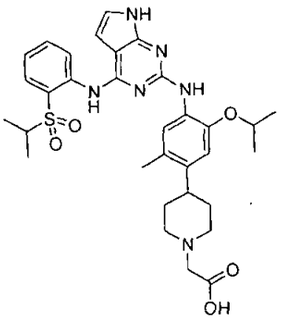
4'-(5-cloro-4-(2-(N,N-dimetilsulfamoil) fenilamino) pirimidin-2-ilamino)-5'-metoxi-N,2'-dimetilbifenil-4-carboxamida

98



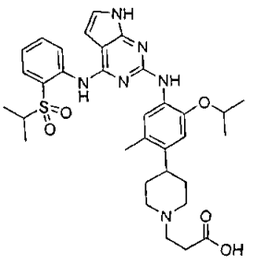
ácido 4'-(5-cloro-4-(2-(N,N-dimetilsulfamoil) fenilamino) pirimidin-2-ilamino)-5'-metoxi-2'-metilbifenil-4-carboxílico

219



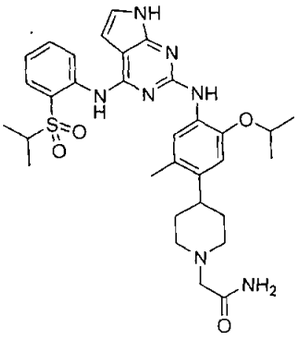
ácido 2-(4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)piperidin-1-il)acético

220



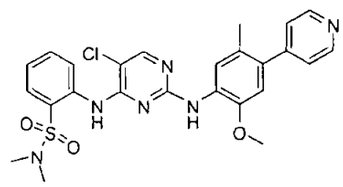
ácido 3-(4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)piperidin-1-il)propanoico

221



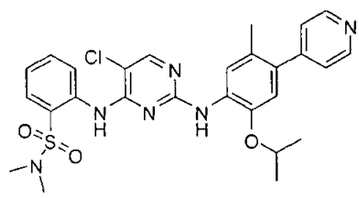
2-(4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)piperidin-1-il)acetamida

99



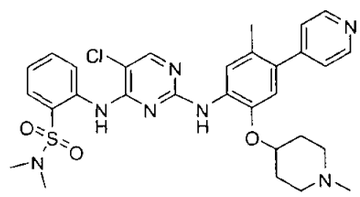
2-(5-cloro-2-(2-metoxi-5-metil-4-(piridin-4-il)fenilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida

100



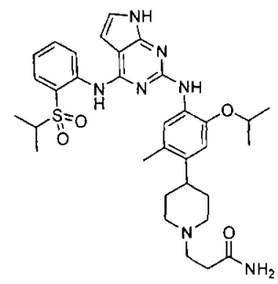
2-(5-cloro-2-(2-isopropoxi-5-metil-4-(piridin-4-il)fenilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida

101



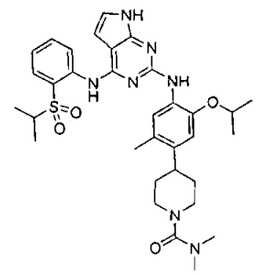
2-(5-cloro-2-(5-metil-2-(1-metilpiperidin-4-iloxi)-4-(piridin-4-il)fenilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida

222



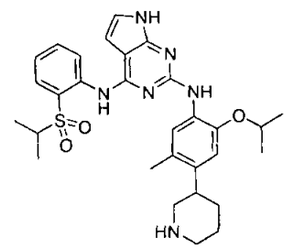
3-(4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)piperidin-1-il)propanamida

223



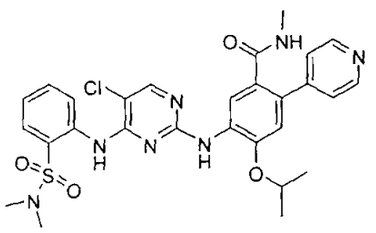
4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)-N,N-dimetilpiperidina-1-carboxamida

224



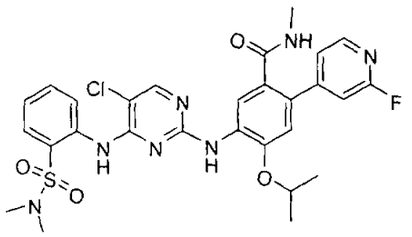
N2-(2-isopropoxi-5-metil-4-(piperidin-3-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina

102



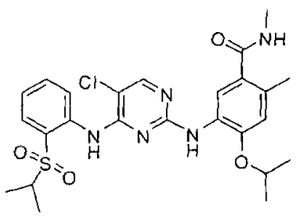
5-(5-cloro-4-(2-(N,N-dimetilsulfamoil) fenilamino) pirimidin-2-ilamino)-4-isopropoxi-N-metil-2-(piridin-4-il)benzamida

103



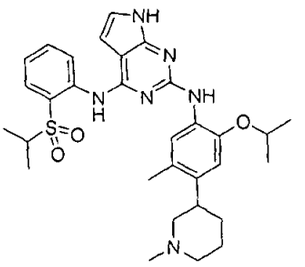
5-(5-cloro-4-(2-(N,N-dimetilsulfamoil) fenilamino) pirimidin-2-ilamino)-2-(2-fluoropiridin-4-il)-4-isopropoxi-N-metilbenzamida

104



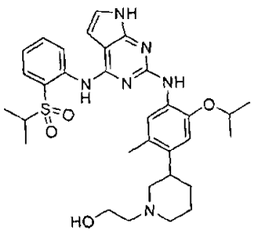
5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N,2-dimetilbenzamida

225



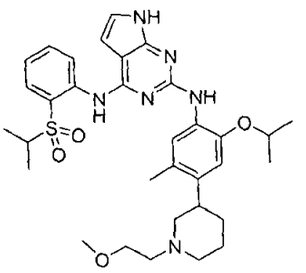
N2-(2-isopropoxi-5-metil-4-(1-metilpiperidin-3-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina

226



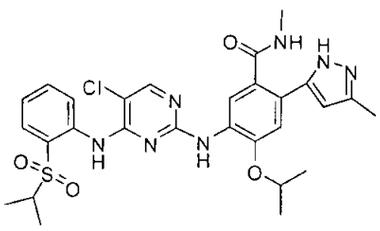
2-(3-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)piperidin-1-il)etanol

227



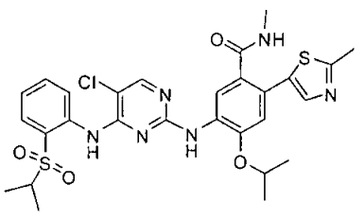
N2-(2-isopropoxi-4-(1-(2-metoxietil)piperidin-3-il)-5-metilfenil)-N4-(2-(isopropilsulfonil) fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina

105



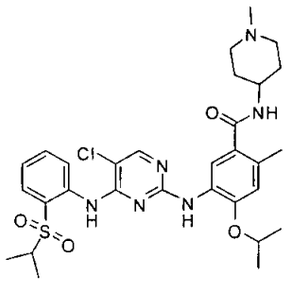
5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metil-2-(3-metil-1H-pirazol-5-il)benzamida

106



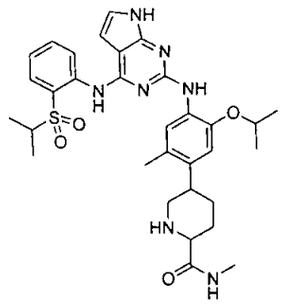
5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-N-metil-2-(2-metiltiazol-5-il)benzamida

107



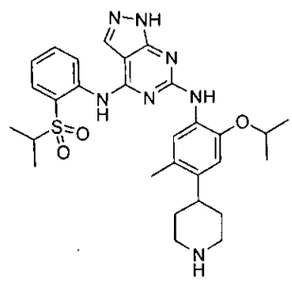
5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-4-isopropoxi-2-metil-N-(1-metilpiperidin-4-il)benzamida

228



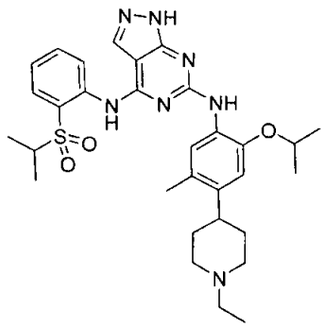
5-(5-isopropoxi-4-(4-(2-(isopropilsulfonil)fenilamino)-7H-pirrolo[2,3-d]pirimidin-2-ilamino)-2-metilfenil)-N-metilpiperidina-2-carboxamida

229



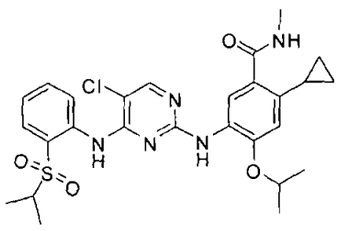
N6-(2-isopropoxi-5-metil-4-(piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil) fenil)-1H-pirazolo[3,4-d]pirimidina-4,6-diamina

230



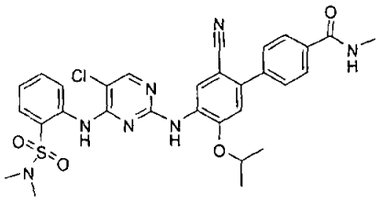
N6-(4-(1-etilpiperidin-4-il)-2-isopropoxi-5-metilfenil)-N4-(2-(isopropilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidina-4,6-diamina

108



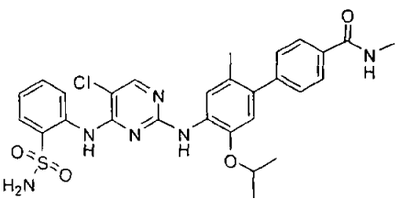
5-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2-ciclopropil-4-isopropoxi-N-metilbenzamida

109



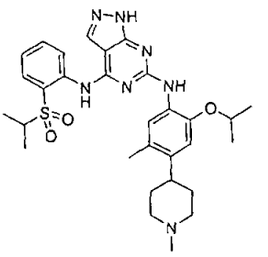
4'-(5-cloro-4-(2-(N,N-dimetilsulfamoil)fenilamino) pirimidin-2-ilamino)-2'-ciano-5'-isopropoxi-N-metilbifenil-4-carboxamida

110



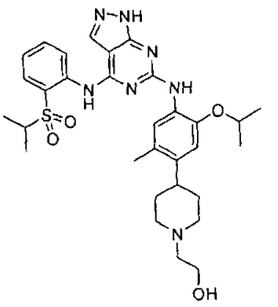
5-cloro-N4-(2-(sulfonilamino)fenil)-N2-(2-metoxi-5-metil-4-(3-metil-4-(metilacetamidofenil)-fenil)pirimidina-2,4-diamina

231



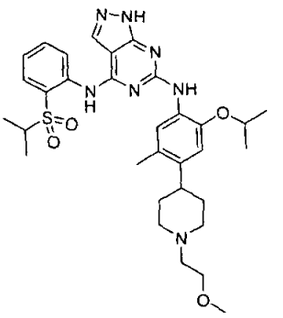
N6-(2-isopropoxi-5-metil-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidina-4,6-diamina

232



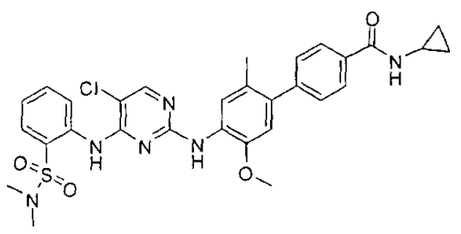
2-(4-(5-isopropoxi-4-(4-(2-(isopropilsulfonil) fenilamino)-1H-pirazolo[3,4-d]pirimidin-6-ilamino)-2-metilfenil)piperidin-1-il)etanol

233



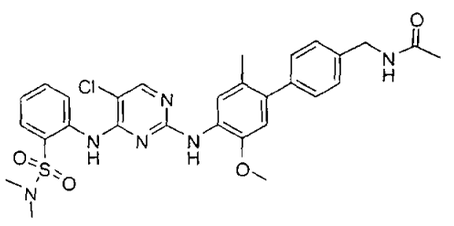
N6-(2-isopropoxi-4-(1-(2-metoxietil) piperidin-4-il)-5-metilfenil)-N4-(2-(isopropilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidina-4,6-diamina

111



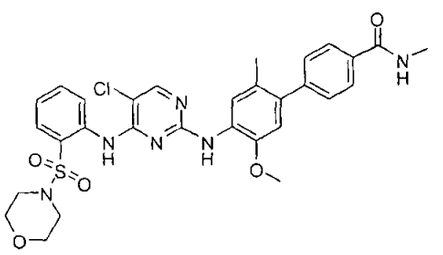
4'-(5-cloro-4-(2-(N,N-dimetilsulfamoil)fenilamino) pirimidin-2-ilamino)-N-ciclopropil-5'-metoxi-2'-metilbifenil-4-carboxamida

112



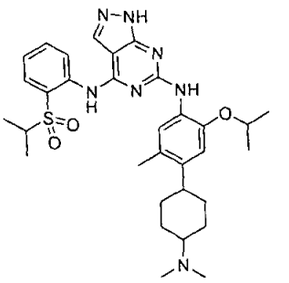
N-((4'-(5-cloro-4-(2-(N,N-dimetilsulfamoil) fenilamino) pirimidin-2-ilamino)-5'-metoxi-2'-metilbifenil-4-il)metil)acetamida

113



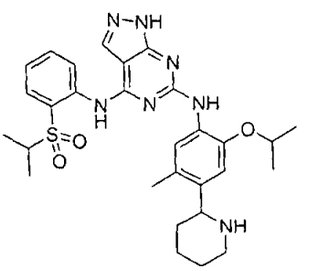
5-cloro-N4-(2-(morfolinosulfonil) fenil)-N2-(2-metoxi-5-metil-4-(4 (metilacetamidofenil)-fenil)pirimidina-2,4-diamina

234



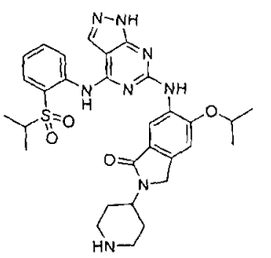
N6-(4-(4-(dimetilamino)ciclohexil)-2-isopropoxi-5-metilfenil)-N4-(2-(isopropilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidina-4,6-diamina

235



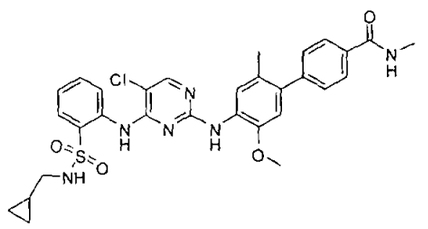
N6-(2-isopropoxi-5-metil-4-(piperidin-2-il)fenil)-N4-(2-(isopropilsulfonil) fenil)-1H-pirazolo[3,4-d]pirimidina-4,6-diamina

236



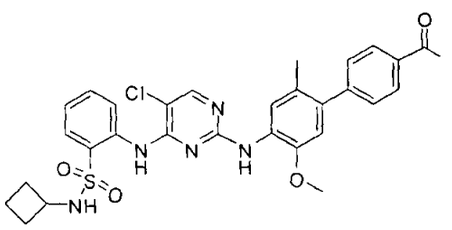
5-isopropoxi-6-(4-(2-(isopropilsulfonil) fenilamino)-1H-pirazolo[3,4-d]pirimidin-6-ilamino)-2-(piperidin-4-il)isoindolin-1-ona

114



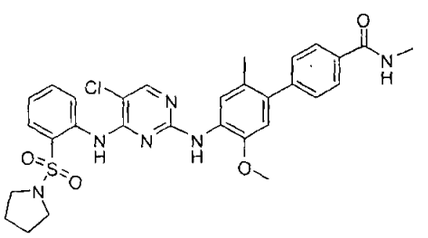
4'-(5-cloro-4-(2-(N-(ciclopropilmetil) sulfamoil)fenilamino)pirimidin-2-ilamino)-5'-metoxi-N,2'-dimetilbifenil-4-carboxamida

115



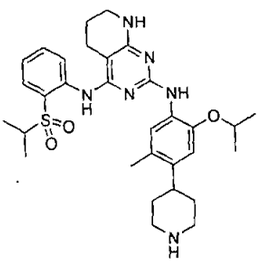
4'-(5-cloro-4-(2-(N-ciclobutil sulfamoil)fenilamino)pirimidin-2-ilamino)-5'-metoxi-N,2'-dimetilbifenil-4-carboxamida

116



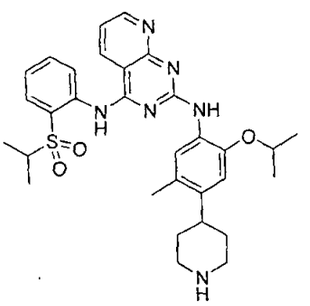
5-cloro-N4-(2-(pirrolidinosulfonil) fenil)-N2-(2-metoxi-5-metil-4-(4-acetamidometilfenil)-fenil)pirimidina-2,4-diamina

237



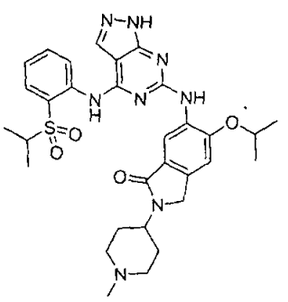
N2-(2-isopropoxi-5-metil-4-(piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil) fenil)-5,6,7,8-tetrahidropirido[2,3-d]pirimidina-2,4-diamina

238



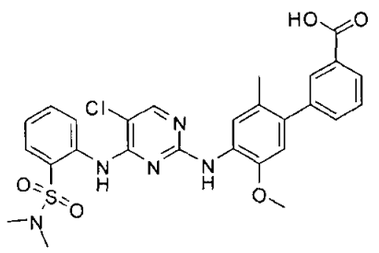
N2-(2-isopropoxi-5-metil-4-(piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil) fenil)pirido[2,3-d]pirimidina-2,4-diamina

239



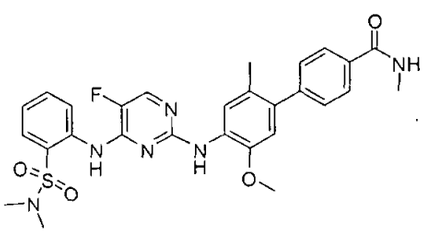
5-isopropoxi-6-(4-(2-(isopropilsulfonil) fenilamino)-1H-pirazolo[3,4-d]pirimidin-6-ilamino)-2-(1-metilpiperidin-4-il)isoindolin-1-ona

117



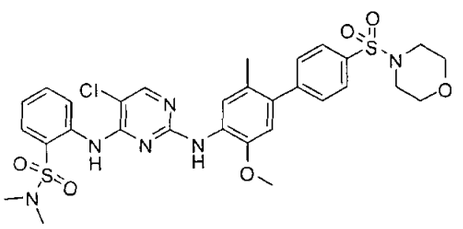
ácido 4'-(5-cloro-4-(2-(N,N-dimetilsulfamoil) fenilamino) pirimidin-2-ilamino)-5'-metoxi-2'-metilbifenil-3-carboxílico

118



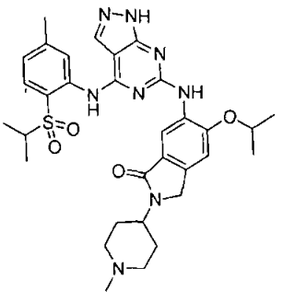
4'-(4-(2-(N,N-dimetilsulfamoil) fenilamino)-5-fluoropirimidin-2-ilamino)-5'-metoxi-N,2'-dimetilbifenil-4-carboxamida

119



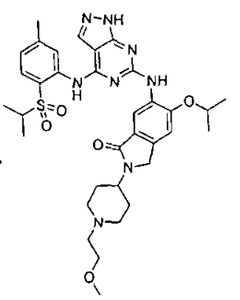
2-(5-cloro-2-(5-metoxi-2-metil-4'-(morfolinosulfonil)bifenil-4-ilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida

240



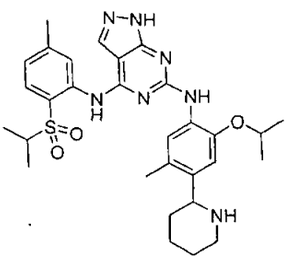
5-isopropoxi-6-(4-(2-(isopropilsulfonil)-5-metilfenilamino)-1H-pirazolo[3,4-d]pirimidin-6-ilamino)-2-(1-metilpiperidin-4-il)isoindolin-1-ona

241



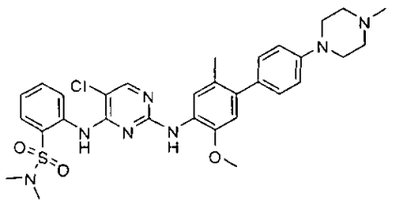
5-isopropoxi-6-(4-(2-(isopropilsulfonil)-5-metilfenilamino)-1H-pirazolo[3,4-d]pirimidin-6-ilamino)-2-(1-(2-metoxi etil)piperidin-4-il)isoindolin-1-ona

242



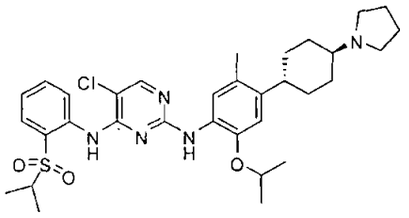
N6-(2-isopropoxi-5-metil-4-(piperidin-2-il)fenil)-N4-(2-(isopropilsulfonil)-5-metilfenil)-1H-pirazolo[3,4-d]pirimidina-4,6-diamina

120



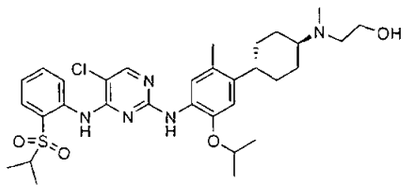
2-(5-cloro-2-(5-metoxi-2-metil-4'-(4-metilpiperazin-1-il)bifenil-4-ilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida

121



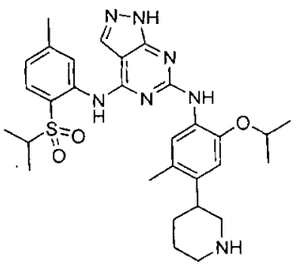
5-cloro-N2-(2-isopropoxi-5-metil-4-((1r,4r)-4-(pirrolidin-1-il)ciclohexil) fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

122



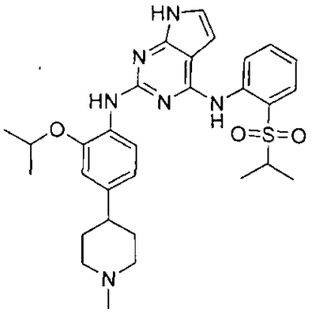
2-(N-((1r,4r)-4-(4-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-5-isopropoxi-2-metilfenil)ciclohexil)-N-metilamino)etanol

243



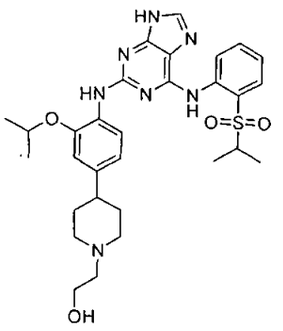
N6-(2-isopropoxi-5-metil-4-(piperidin-3-il)fenil)-N4-(2-(isopropilsulfonil)-5-metilfenil)-1H-pirazolo[3,4-d]pirimidina-4,6-diamina

244



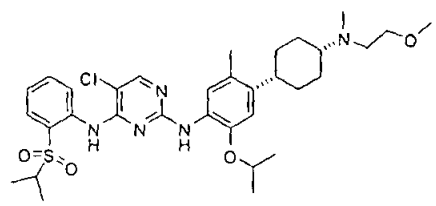
N2-(2-isopropoxi-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil) fenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina

245



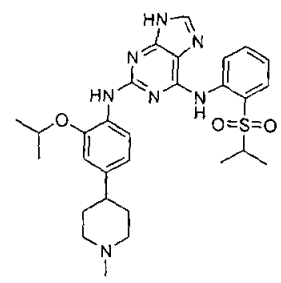
2-(4-(3-isopropoxi-4-(6-(2-(isopropilsulfonil) fenilamino)-9H-purin-2-ilamino)fenil)piperidin-1-il)etanol; y

123



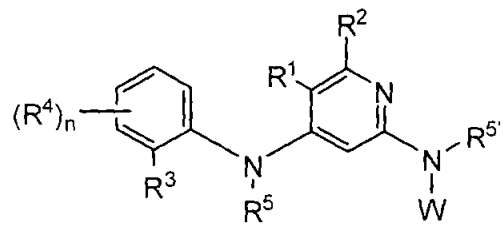
N2-(4-((1s,4s)-4-(N-(2-metoxietil)-N-metilamino)ciclohexil)-2-isopropoxi-5-metilfenil)-5-cloro-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

246



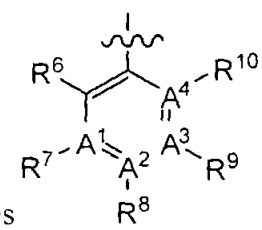
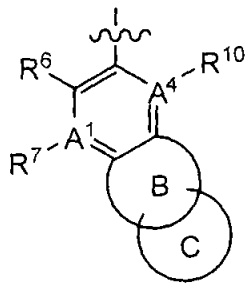
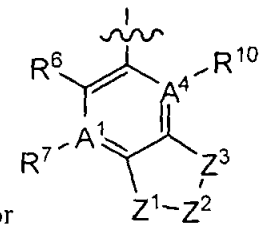
N2-(2-isopropoxi-4-(1-metilpiperidin-4-il)fenil)-N6-(2-(isopropilsulfonil) fenil)-9H-purina-2,6-diamina.

12. Un compuesto que tiene la Fórmula (5):



(5)

o sales farmacéuticamente aceptables del mismo; donde

W es  ,  or  ;

A^1 y A^4 son independientemente C o N;

cada A^2 y A^3 es C, o uno de A^2 y A^3 es N donde R^6 y R^7 forman un anillo;

B y C son independientemente un anillo carbocíclico de 5-7 miembros opcionalmente sustituido, aril, heteroaril o un anillo heterocíclico que contiene N, O o S;

Z^1, Z^2 y Z^3 son independientemente NR^{11}, C=O, CR-OR, $(CR_2)_{1-2}$ o =C-R^{12};

R^1 y R^2 son independientemente halo, OR^{12}, $NR(R^{12})$, SR^{12}, o un C_{1-6} alquil, C_{2-6} alquenil o C_{2-6} alquinil, opcionalmente sustituidos; o uno de R^1 y R^2 es H;

R^3 es $(CR_2)_{0-2}SO_2R^{12}$, $(CR_2)_{0-2}SO_2NRR^{12}$, $(CR_2)_{0-2}CO_{1-2}R^{12}$, $(CR_2)_{0-2}CONRR^{12}$ o ciano;

R^4, R^6, y R^7 y R^{10} cuyo están unidos a un átomo de carbono, son independientemente H, un C_{1-6} alquil, C_{2-6} alquenil o C_{2-6} alquinil, opcionalmente sustituidos; OR^{12}, $NR(R^{12})$, halo, nitro, SO_2R^{12}, $(CR_2)_pR^{13}$ o X; siempre que R^6 y R^7 no son ambos H;

R, R^5 y $R^{5'}$ son independientemente H o C_{1-6} alquil;

R^8 y R^9 son independientemente C_{1-6} alquil, C_{2-6} alquenil, C_{2-6} alquinil, halo o X, o uno de R^8 y R^9 es H; y siempre que uno de R^8 y R^9 es X;

alternativamente, R^1 y R^2, o R^6 y R^7, R^7 y R^8, o R^9 y R^{10}, cuyo están unidos a un átomo de carbono puede formar un anillo carbocíclico monocíclico o fusionado de 5-7 miembros opcionalmente sustituido, aril, o heteroaril o un anillo heterocíclico que comprende N, O y/o S; o R^7, R^8, R^9 y R^{10} están ausentes cuyo están unidos a un N;

R^{11} es H, C_{1-6} alquil, C_{2-6} alquenil, $(CR_2)_pCO_{1-2}R$, $(CR_2)_pOR$, $(CR_2)_pR^{13}$, $(CR_2)_pNRR^{12}$, $(CR_2)_pCONRR^{12}$ o $(CR_2)_pSO_{1-2}R^{12}$;

R^{12} y R^{13} son independientemente un anillo carbocíclico de 3-7 miembros saturado o parcialmente insaturado opcionalmente sustituido, o un anillo heterocíclico de 5-7 miembros que comprende N, O y/o S; aril o heteroaril; o R^{12} es H, C_{1-6} alquil;

X es $(CR_2)_qY$, ciano, $CO_{1-2}R^{12}$, $CONR(R^{12})$, $CONR(CR_2)_pNR(R^{12})$, $CONR(CR_2)_pOR^{12}$, $CONR(CR_2)_pSR^{12}$, $CONR(CR_2)_pS(O)_{1-2}R^{12}$ o $(CR_2)_{1-6}NR(CR_2)_pOR^{12}$;

Y es un anillo carbocíclico de 3-12 miembros opcionalmente sustituido, un aril de 5-12 miembros, o un heteroaril de 5-12 miembros o un anillo heterocíclico que comprende N, O y/o S y unidos a un^2 o A^3 o ambos por medio de un átomo de carbono de dicho heteroaril o un anillo heterocíclico donde q en $(CR_2)_qY$ es 0; y

n, p y q son independientemente 0-4.

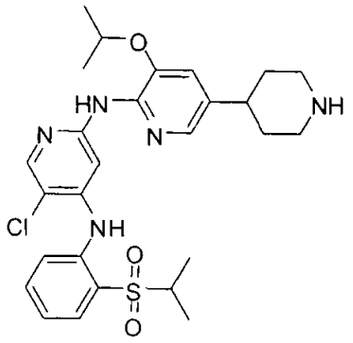
13. El compuesto de la Reivindicación 12, donde R^1 es halo o C_{1-6} alquil;

R^2 es H o NH_2; or

R^1 y R^2 juntos forman un anillo de 5-6 miembros arílico, o heteroarílico o heterocíclico opcionalmente sustituido que comprende 1-3 átomos de nitrógeno.

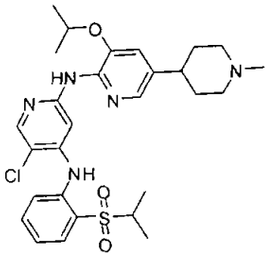
14. El compuesto de la Reivindicación 12, seleccionado del grupo que consiste en

247



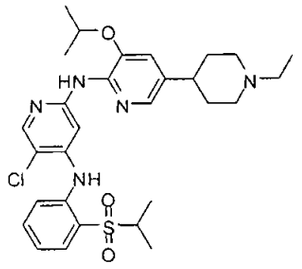
5-cloro-N2-(3-isopropoxi-5-(piperidin-4-il)piridin-2-il)-N4-(2-(isopropilsulfonil) fenil)piridina-2,4-diamina

248



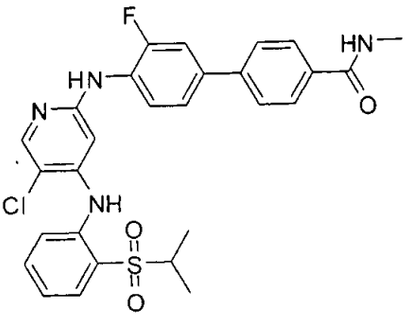
5-cloro-N2-(3-isopropoxi-5-(1-metilpiperidin-4-il)piridin-2-il)-N4-(2-(isopropilsulfonil) fenil)piridina-2,4-diamina

249



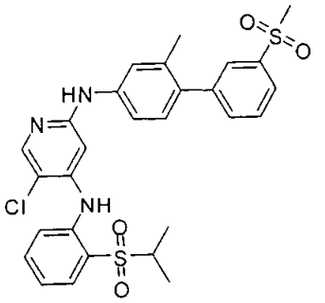
5-cloro-N2-(5-(1-etilpiperidin-4-il)-3-isopropoxipiridin-2-il)-N4-(2-(isopropilsulfonil) fenil)piridina-2,4-diamina

252



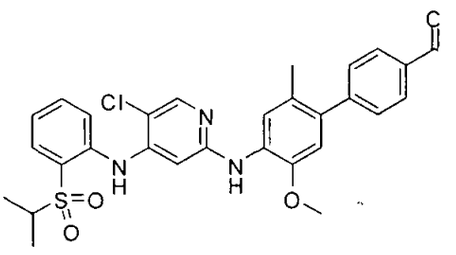
4'-(5-cloro-4-(2-(isopropilsulfonil) fenilamino) piridin-2-ilamino)-3'-fluoro-N-metilbifenil-4-carboxamida

253



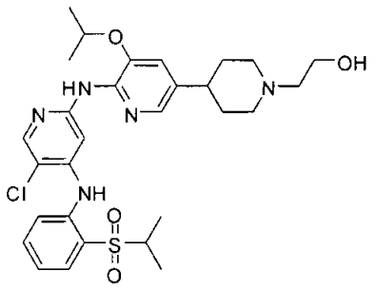
5-cloro-N4-(2-(isopropilsulfonil)fenil)-N2-(2-metil-3'-(metilsulfonil)bifenil-4-il)piridina-2,4-diamina

254



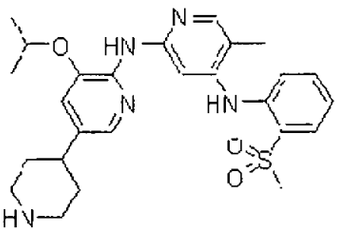
Metil 4'-(5-cloro-4-(2-(isopropilsulfonil) fenilamino)piridin-2-ilamino)-5'-metoxi-2'-metilbifenil-4-carboxilato

250



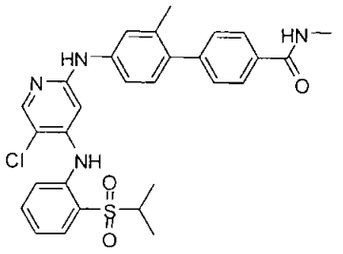
2-(4-(6-(5-cloro-4-(2-(isopropilsulfonil) fenilamino)piridin-2-ilamino)-5-isopropoxipiridin-3-il)piperidin-1-il)etanol

255



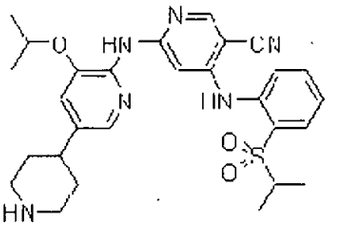
N2-(3-isopropoxi-5-(piperidin-4-il)piridin-2-il)-5-metil-N4-(2-(metilsulfonil)fenil)piridina-2,4-diamina; y

251



4'-(5-cloro-4-(2-(isopropilsulfonil) fenilamino) piridin-2-ilamino)-N,2'-dimetilbifenil-4-carboxamida

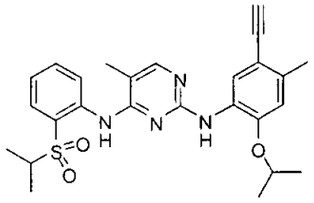
256



6-(3-isopropoxi-5-(piperidin-4-il)piridin-2-ilamino)-4-(2-(isopropilsulfonil) fenilamino) nicotinonitrilo.

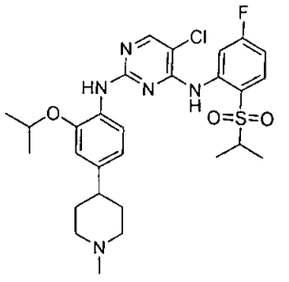
15. Un compuesto seleccionado del grupo que consiste en

257



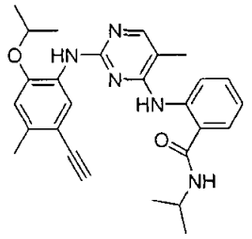
N2-(5-Etinil-2-isopropoxi-4-metil-fenil)-5-metil-N4-[2-(propano-2-sulfonil)-fenil]-pirimidina-2,4-diamina

274



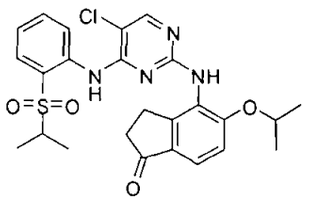
5-cloro-N4-(5-fluoro-2-(isopropilsulfonil) fenil)-N2-(2-isopropoxi-4-(1-metil piperidin-4-il)fenil)pirimidina-2,4-diamina

258



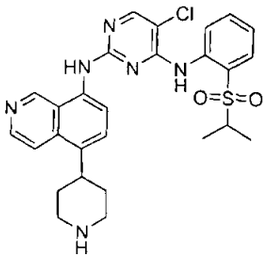
2-(2-(5-etinil-2-isopropoxi-4-metilfenilamino)-5-metilpirimidin-4-ilamino)-N-isopropilbenzamida

259



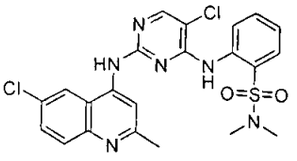
4-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-2,3-dihidro-5-isopropoxiinden-1-ona

260



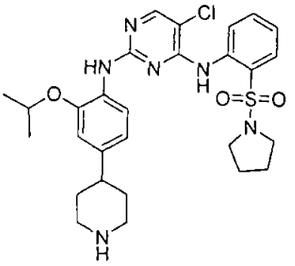
5-cloro-N4-(2-(isopropilsulfonil) fenil)-N2-(5-(piperidin-4-il)isoquinolin-8-il)pirimidina-2,4-diamina

261



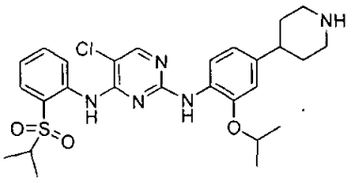
2-[5-Cloro-2-(6-cloro-2-metil-quinolin-4-ilamino)-pirimidin-4-ilamino]-N,N-dimetil-bencenosulfonamida

275



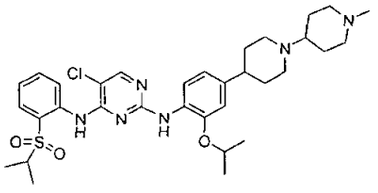
5-cloro-N2-(2-isopropoxi-4-(piperidin-4-il)fenil)-N4-(2-(pirrolidin-1-ilsulfonil)fenil)pirimidina-2,4-diamina

276



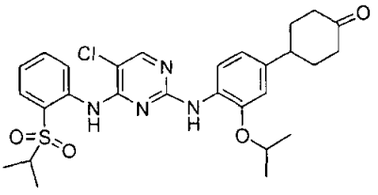
5-cloro-N2-(2-isopropoxi-4-(piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

277



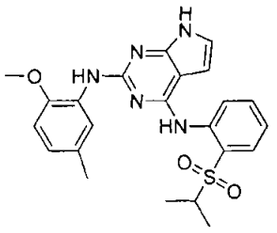
5-cloro-N2-(2-isopropoxi-4-(1-(1-metilpiperidin-4-il)piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

278



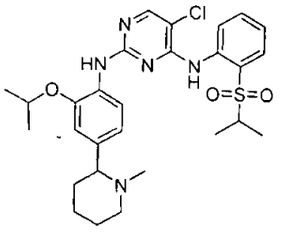
4-(4-(4-(2-(isopropilsulfonil)fenilamino)-5-cloropirimidin-2-ilamino)-3-isopropoxifenil)ciclohexanona

262



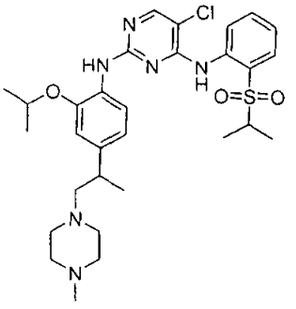
N4-(2-(isopropilsulfonil)fenil)-N2-(2-metoxi-5-metilfenil)-7H-pirrolo[2,3-d]pirimidina-2,4-diamina

263



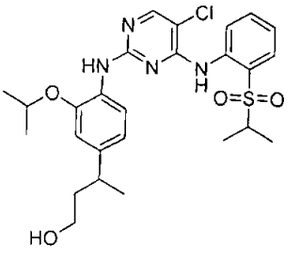
5-cloro-N2-(2-isopropoxi-4-(1-metil piperidin-2-il)fenil)-N4-(2-(isopropil sulfonil)fenil)pirimidina-2,4-diamina

264



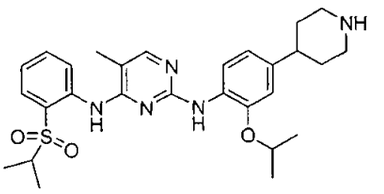
5-cloro-N2-(2-isopropoxi-4-(1-(4-metilpiperazin-1-il)propan-2-il)fenil)-N4-(2-(isopropilsulfonil)fenil) pirimidina-2,4-diamina

265



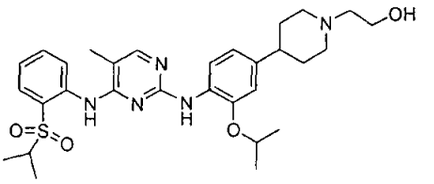
3-(4-(5-cloro-4-(2-(isopropilsulfonil) fenilamino) pirimidin-2-ilamino)-3-isopropoxifenil)butan-1-ol

279



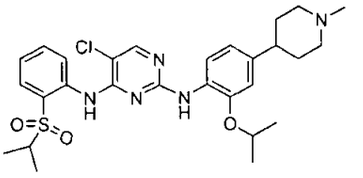
N2-(2-isopropoxi-4-(piperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-5-metilpirimidina-2,4-diamina

280



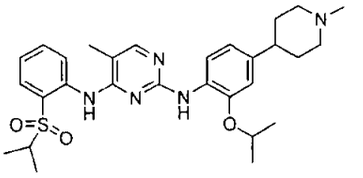
2-(4-(4-(4-(2-(isopropilsulfonil)fenilamino)-5-metilpirimidin-2-ilamino)-3-isopropoxi fenil)piperidin-1-il)etanol

281



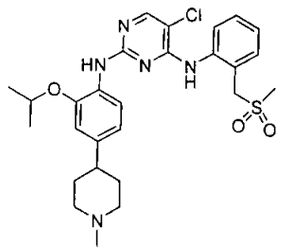
5-cloro-N2-(2-isopropoxi-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina

282



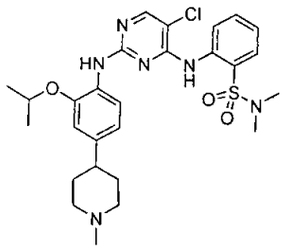
N2-(2-isopropoxi-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(isopropilsulfonil)fenil)-5-metilpirimidina-2,4-diamina

266



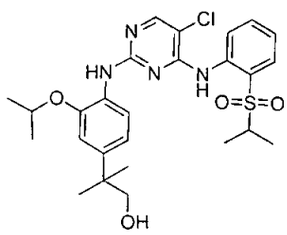
5-cloro-N2-(2-isopropoxi-4-(1-metilpiperidin-4-il)fenil)-N4-(2-(metilsulfonilmetil) fenil)pirimidina-2,4-diamina

267



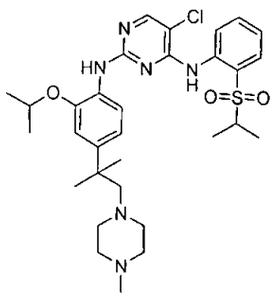
2-(5-cloro-2-(2-isopropoxi-4-(1-metil piperidin-4-il)fenilamino) pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida

268



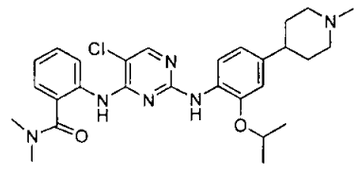
2-(4-(5-cloro-4-(2-(isopropilsulfonil) fenilamino) pirimidin-2-ilamino)-3-isopropoxifenil)-2-metilpropan-1-ol

269



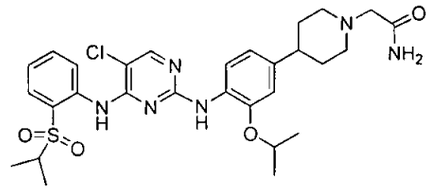
5-cloro-N2-(2-isopropoxi-4-(2-metil-1-(4-metilpiperazin-1-il)propan-2-il)fenil)-N4-

283



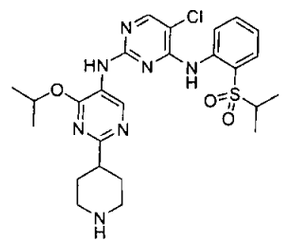
2-(2-(2-isopropoxi-4-(1-metilpiperidin-4-il)fenilamino)-5-cloropirimidin-4-ilamino)-N,N-dimetilbenzamida

284



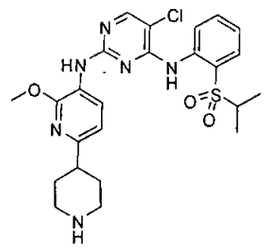
2-(4-(4-(4-(2-(isopropilsulfonil) fenilamino)-5-cloropirimidin-2-ilamino)-3-isopropoxifenil) piperidin-1-il)acetamida

285



5-cloro-N2-(4-isopropoxi-2-(piperidin-4-il)pirimidin-5-il)-N4-(2-(isopropil sulfonil)fenil)pirimidina-2,4-diamina

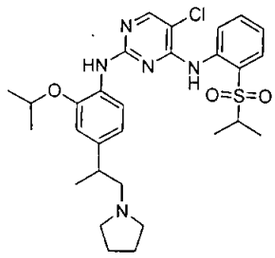
286



5-cloro-N4-(2-(isopropilsulfonil)fenil)-N2-(2-metoxi-6-(piperidin-4-il)piridin-3-il)

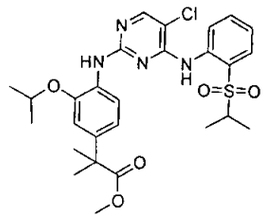
(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

270



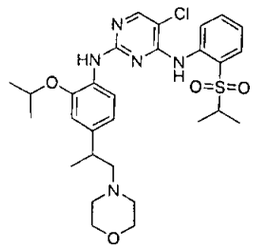
5-cloro-N2-(2-isopropoxi-4-(1-(pirrolidin-1-il)propan-2-il)fenil)-N4-(2-(isopropilsulfonil) fenil)pirimidina-2,4-diamina

271



Metil 2-(4-(5-cloro-4-(2-(isopropilsulfonil) fenilamino)pirimidin-2-ilamino)-3-isopropoxifenil)-2-metilpropanoato

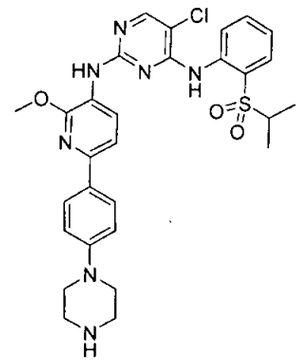
272



5-cloro-N2-(2-isopropoxi-4-(1-morfolinopropan-2-il)fenil)-N4-(2-(isopropilsulfonil)fenil)pirimidina-2,4-diamina

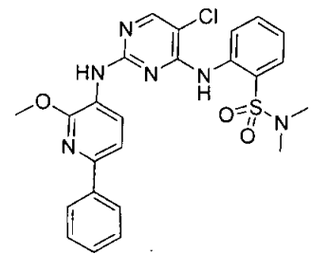
pirimidina-2,4-diamina

287



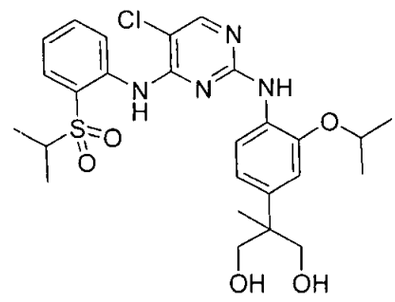
5-cloro-N4-(2-(isopropilsulfonil)fenil)-N2-(2-metoxi-6-(4-(piperazin-1-il)fenil)piridin-3-il)pirimidina-2,4-diamina

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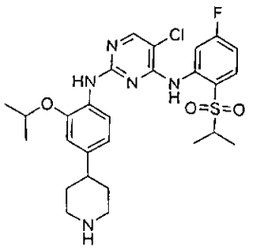
2-(5-cloro-2-(2-metoxi-6-fenilpiridin-3-ilamino)pirimidin-4-ilamino)-N,N-dimetilbencenosulfonamida; y

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2-(4-(5-cloro-4-(2-(isopropilsulfonil)fenilamino) pirimidin-2-ilamino)-3-isopropoxifenil)-2-metilpropano-1,3-diol.

273



5-cloro-N4-(5-fluoro-2-(isopropilsulfonil)fenil)-N2-(2-isopropoxi-4-(piperidin-4-il)fenil)pirimidina-2,4-diamina

16. Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de cualquiera de las reivindicaciones 1-15 y un portador farmacéuticamente aceptable.

17. Un método para inhibir la quinasa del linfoma anaplásico, que comprende una célula o un sistema de tejidos o a un sujeto mamífero, una cantidad terapéuticamente eficaz de un compuesto de cualquiera de las reivindicaciones 1-15, o sus sales farmacéuticamente aceptables, así ihnibiendo dicha quinasa.

18. El uso de un compuesto de cualquiera de las reivindicaciones 1-15, o de una composición farmacéutica, para la fabricación de un medicamento para el tratamiento de una enfermedad mediada por la quinasa del linfoma anaplásico, y opcionalmente en combinación con un segundo agente terapéutico, en el que dicha condición es una enfermedad autoinmune, una enfermedad de transplante, una enfermedad infecciosa o un trastorno de proliferación celular.

19. El uso de un compuesto de cualquiera de las reivindicaciones 1-15, o de una composición farmacéutica, para la fabricación de un medicamento para el tratamiento de un trastorno de proliferación celular y, opcionalmente, en combinación con un segundo agente terapéutico, en el que dicho trastorno proliferativo es linfoma, osteosarcoma, melanoma, o un tumor de mama, renal, de próstata, colorrectal, tiroides, ovario, páncreas, neuronales, pulmón, uterino o gastrointestinal.

20. El uso de la reivindicación 19, donde dicho segundo agente terapéutico es a un agente quimioterapéutico.

Resumen

La invención proporciona nuevos derivados de pirimidina y piridina y composiciones farmacéuticas, y métodos para el uso de dichos compuestos. Por ejemplo, derivados de pirimidina y piridina de la invención pueden ser utilizados para tratar, aliviar o prevenir una condición que responda a la inhibición de la actividad de la quinasa del linfoma anaplásico (ALK), la quinasa de adhesión focal (FAK), la proteína quinasa 70 asociada a la cadena zeta (ZAP-70), el factor de crecimiento tipo insulina (IGF-1R), o una combinación de éstos.

PATENT COOPERATION TREATY PCT/US2007/085304

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

TONGCO WU, Emily
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)* 25 May 2009 (25.05.2009)	
Applicant's or agent's file reference P1283PC10	IMPORTANT NOTIFICATION
International application No PCT/US2007/085304	International filing date *(day/month/year)* 20 November 2007 (20.11.2007)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
IRM LLC Hurst Holme 12 Trott Road Hamilton, HM 11 Bermuda	US	
	Telephone No. 858-812-1539	
	Facsimile No 858-812-1909	
	E-mail address etongcowu@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	State of Nationality	State of Residence
IRM LLC 131 Front Street P.O. Box 2899 Hamilton, HM LX Bermuda	US	
	Telephone No. 858-812-1539	
	Facsimile No. 858-812-1909	
	E-mail address etongcowu@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 87 40	Authorized officer Boccard Paulette e-mail pt01.pct@wipo.int Telephone No. +41 22 338 74 01

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference P1283PC10	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2007/085304	International filing date *(day/month/year)* 20 November 2007 (20.11.2007)	Priority date *(day/month/year)* 08 December 2006 (08.12.2006)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant IRM LLC		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 10 June 2009 (10.06.2009)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Dorothée Mülhausen
Facsimile No. +41 22 338 82 70	e-mail: pt01.pct@wipo.int

Form PCT/IB/373 (January 2004)

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/US2007/085304	20.11.2007	08.12.2006

International Patent Classification (IPC) or both national classification and IPC
INV. C07D213/74 C07D239/48 C07D239/95 C07D401/12 C07D401/14 C07D403/12 C07D403/14 C07D413/12 C07D417/12 C07D451/02 C07D453/02 C07D471/04 C07D473/16 C07D487/04 C07D487/08 A61K31/506

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 Tx: 523656 epmu d* Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Kirsch, Cécile Telephone No. +49 89 2399-2191

Form (PCT/ISA/237) (Cover Sheet) (April 2005)

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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. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 17

because:

☒ the said international application, or the said claims Nos. 17 relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☐ not paid additional fees

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V *Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement*

1. Statement

Novelty (N)	Yes:	Claims	11-15
	No:	Claims	1-10, 16-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-16,18-20
	No:	Claims	

2. Citations and explanations

see separate sheet

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

D1: WO 2006/021454
D2: WO 2005/016894
D3: WO 2004/080980

The present application deals with 4-phenylamino-2-arylamino-pyrimidine or -pyridine derivatives as protein kinase inhibitors (ALK, FAK, ZAP70, IGF1R) for treating autoimmune diseases, transplantation diseases, infectious diseases or cell proliferative disorders.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 17 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

The attention of the applicant is drawn to the fact that the only structural element common to all the compounds claimed is the presence of a 6-membered aromatic ring containing at least one nitrogen atom and substituted in 4-position with a 2-substituted phenylamino group and in 2-position with a (6-membered aromatic ring)amino moiety. Such a structural feature is already disclosed in document D1 for compounds which exhibit the same biological activity. All the other structural elements according to formula (I) vary. Since the common feature is not novel, it cannot represent the single inventive concept which could have linked the different claimed subject-matters together.

The technical relationship between the different subject-matters of claims 1-20 required by rules 13.1 PCT lacks and the requirement for unity of invention referred to in Article 17.3(a) PCT is not fulfilled.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Novelty

1.1. Document D1-D3 disclose 4-phenylamino-2-arylamino-pyrimidine derivatives as protein kinase inhibitors (ALK, FAK, ZAP70, IGF1R) for treating immune diseases or cell proliferative disorders.

1.2. On the basis of claim 1, it turns out that there is an overlap between the claimed subject-matter and the teaching of D1-D3 and the applicant has not defined in which way this overlap could be regarded as novel vis-à-vis D1-D3, that is to say, the applicant has not defined the new technical element common to the compounds of the present application which fall within the overlap and which can be regarded as adding a new element to the state of the art.

1.3 As stated above, the only structural element common to all the compounds claimed is the presence of a 6-membered aromatic ring containing at least one nitrogen atom and substituted in 4-position with a 2-substituted phenylamino group and in 2-position with a (6-membered aromatic ring)amino moiety. All the other structural elements vary and no common feature could be identified between the claimed alternatives. Since, the new technical feature, which is necessary to established novelty, fails, the overlap is considered identical to what has already been disclosed in D1-D3 (Article 33(2) PCT).

Attention is drawn to the fact that the content of D1-D3 is neither limited to its examples nor to the preferred embodiments disclosed therein. The content of these documents should be regarded as a whole and all the information contained therein is state of the art in the sense of Article 33(2) PCT.

2. Inventive step

2.1. Documents D1 and D2 may be considered as the closest prior art since their scope overlaps with the present claimed subject-matter. The difference between the

compounds of the prior art and the compounds presently claimed is that the claimed compounds are generically described in the prior art.

2.2. The problem to be solved by the present invention may therefore be considered as the provision of further 4-phenylamino-2-arylamino-pyrimidine derivatives as protein kinase inhibitors (ALK, FAK, ZAP70, IGF1R) for treating immune diseases or cell proliferative disorders.

2.3. Since no precise biological data about the actual physiological properties of claimed compounds have been provided by the applicant, it is not clear if the problem had actually been solved or not. Consequently, the applicant is invited to submit all information available to him to substantiate that all claimed compounds are a solution to the problem underlying the current application or, if necessary to restrict the claims to the compounds which illustrate reasonable patentable effects (to be shown).

2.4. Starting from D1 or D2, it appears that all the compounds claimed therein are expected to exhibit the claimed activity as long as the characteristic core structure is present. The indiscriminate selection of some defined compounds among many is prima facie obvious. The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity. One skilled in the art would thus be motivated to prepare products embraced by the prior art to arrive at the instant claimed products with the expectation of obtaining additional beneficial products which would be useful in treating, for example, cancer.

In this context, attention is drawn to the fact that it is well-known in the field of drug design that structurally similar molecules possess similar biological activities. Indeed, small structural modifications within a core structure known for its biological activity come within the scope of the customary practice followed by persons skilled in the art to provide new active compounds. In the present case, the compounds exemplified in D1 and D2 are structurally very close to the present claimed compounds. Such changes within a known active structure are considered to stay within a common practice in the field of drug design.

Therefore, the mere selection of a specific family of compound within a broader group

known for its biological activity cannot be considered inventive in the sense of Art. 56 EPC since there is a clear indication for the skilled to seek in this direction.

3. Industrial applicability

For the assessment of the present claim 17 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor are these documents identified therein.

2. The vague and imprecise statement in the description on page 145 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in a lack of clarity of the claims (Article 6 PCT) when the description is used to interpret the claims. This statement should therefore be amended to remove this inconsistency.

3. The expression "which is hereby incorporated by reference" as well as similar expressions should be deleted from the description.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 June 2008 (19.06.2008)

PCT

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WO 2008/073687 A3

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C07D 213/74 (2006.01) *C07D 417/12* (2006.01)
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C07D 239/95 (2006.01) *C07D 453/02* (2006.01)
C07D 401/12 (2006.01) *C07D 471/04* (2006.01)
C07D 401/14 (2006.01) *C07D 473/16* (2006.01)
C07D 403/12 (2006.01) *C07D 487/04* (2006.01)
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C07D 413/12 (2006.01)

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20 November 2007 (20.11.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/869,299 8 December 2006 (08.12.2006) US
60/966,449 28 August 2007 (28.08.2007) US

(71) Applicant *(for all designated States except US)*: **IRM LLC** [US/—]; Hurst Holme, 12 Trott Road, Hamilton, HM 11 (BM).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MICHELLYS, Pierre-Yves** [FR/US]; 1416 Corte Bravo, San Marcos, CA 92069 (US). **PEI, Wei** [CN/US]; 8688 New Salem Street, Unit 184, San Diego, CA 92126 (US). **MARSILJE, Thomas H.** [US/US]; 1844 Narragansett Court, San Diego, CA 92107 (US). **LU, Wenshuo** [CA/US]; 7594 Wallingford Court, San Diego, CA 92126 (US). **CHEN, Bei** [CN/US]; 11048 Creekbridge Place, San Diego, CA 92128 (US). **UNO, Tetsuo** [JP/US]; 4495 Shorepoint Way, San Diego, CA 92130 (US). **JIN, Yunho** [KR/US]; 13447 Tiverton Road, San Diego, CA 92130 (US). **JIANG, Tao** [CN/US]; 10721 Calle Mar de Mariposa, San Diego, CA 92130 (US).

(74) Agents: **TONGCO WU, Emily** 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, 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, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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31 July 2008

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

(57) Abstract: The invention provides novel pyrimidine and pyridine derivatives of formula (I) and pharmaceutical compositions thereof, and methods for using such compounds. For example, the pyrimidine and pyridine derivatives of the invention may be used to treat, ameliorate or prevent a condition which responds to inhibition of anaplastic lymphoma kinase (ALK) activity, focal adhesion kinase (FAK), zeta-chain-associated protein kinase 70 ZAP-70), insulin-like growth factor (IGF- 1R), or a combination thereof.

WO 2008/073687 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/085304

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/74 C07D239/48 C07D239/95 C07D401/12 C07D401/14
C07D403/12 C07D403/14 C07D413/12 C07D417/12 C07D451/02
C07D453/02 C07D471/04 C07D473/16 C07D487/04 C07D487/08

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, BEILSTEIN Data, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/021454 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; IMBACH PATRICIA [CH]; KAW) 2 March 2006 (2006-03-02) Claims 1-12; Formula (I); examples especially 32-33, 36, 39, 48	1-20
X	WO 2005/016894 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; IRM LLC; GARCIA-ECHEVERRI) 24 February 2005 (2005-02-24) Claims 1-22; Formula (I); examples especially 20-12 and 20-13, 344, 348, 350, 355, 359, 366, 371, 377	1-20

-/--

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 May 2008	04/06/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kirsch, Cécile

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/085304

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/080980 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; GARCIA-ECHEVERRIA CARLOS) 23 September 2004 (2004-09-23) Claims 1-22; Formula (I); examples especially 20-12 and 20-13	1-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/085304

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 17 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/085304

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006021454 A	02-03-2006	AR 054081 A1	06-06-2007
		AU 2005276582 A1	02-03-2006
		CA 2577251 A1	02-03-2006
		CN 101048386 A	03-10-2007
		EP 1784392 A2	16-05-2007
		HR 20070076 A2	31-07-2007
		JP 2008510763 T	10-04-2008
		KR 20070054223 A	28-05-2007
WO 2005016894 A	24-02-2005	AU 2004264382 A1	24-02-2005
		BR PI0413616 A	17-10-2006
		CA 2533320 A1	24-02-2006
		EP 1660458 A1	31-05-2006
		IS 8349 A	13-03-2006
		JP 2007502260 T	08-02-2007
		KR 20060039938 A	09-05-2006
		MX PA06001759 A	12-05-2006
WO 2004080980 A	23-09-2004	AU 2004220338 A1	23-09-2004
		BR PI0408347 A	21-03-2006
		CA 2518932 A1	23-09-2004
		CN 1788001 A	14-06-2006
		EP 1606265 A1	21-12-2005
		IS 8062 A	06-10-2005
		JP 2006520354 T	07-09-2006
		KR 20050109987 A	22-11-2005
		MA 27668 A1	01-12-2005
		MX PA05009883 A	05-12-2005
		US 2006247241 A1	02-11-2006

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MÍNIMOS PARA ADMISIÓN A TRAMITE
PCT

PATENTE DE INVENCIÓN [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fec

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-070739- -00000-0000
Fecha. 2009-07-08 17:00:29 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve 378 FASENACIONALI
Act 411 PRESENTACION Folios: 418

Carrera 13 No. 27-00 Piso 5,7y10´
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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
IRM LLC

REFERENCIA	Radicación No.	9 70739
	Solicitud internacional	PCT/US2007/085304
	Fecha inicio fase nacional	08/07/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	№ 08155

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. 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.

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.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 17 JUL. 2009
adpa11

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
IRM LLC

REFERENCIA	Radicación No.	9 70739
	Solicitud internacional	PCT/US2007/085304
	Fecha inicio fase nacional	08/07/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	№ 08156

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de quince reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 17 JUL. 2009.
adpa11