PCT

Industria y Comercio

SUPERINTENDENCIA

11-8053

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO INVENTARIO

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-008053- -00000-0000
Fecha: 2011-01-25 17:07:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 334

TITULO: DERIVADOS DE PIRIMIDINA COMO INHIBIDORES DE CINASA

SOLICITANTE: IRM LLC

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

APODERADO: CARLOS R. OLARTE

BOGOTÁ 25 de Enero de 2011

P2011/000017

25-01-2011

OLARTE MOURE

OLARTE MOURE & AS

Industria y Comercio
SUPERINTENDENCIA

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No. 11-008053- -00000-0000
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PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2011/000017**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

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Nacionalidad o Domicilio: Bermuda
Lugar de Constitución: Bermuda

Teléfono: _____ **Fax:** _____
E-mail: _____

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

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Número 79782747Bta
TP 74.295

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(5) **PCT (86)**

Solicitud Internacional No. PCT/US2009/048428 Fecha Junio 24, 2009

Publicación Internacional No. WO 2010/002655 Fecha Enero 7, 2010

(6) **Título (54)** **DERIVADOS DE PIRIMIDINA COMO INHIBIDORES DE CINASA**

Clasificación Internacional (51) C07D 401/14, C07D 403/12, C07D 403/14, C07D 409/14, C07D 413/14, A61K 31/506

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

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US	Junio 25, 2008	61/075.583
US	Febrero 25, 2009	61/155.434

(9) **Comprobante de pago No.** 11- **Fecha** Enero 25, 2011

ANEXOS

2

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

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

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Nacionalidad: China

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 006915

Bogotá D.C., Enero 25 de 2011 - 16:30:03

RECIBIDO DE : OLARTERAISBECK NI 830.122.870

*** Soporte del Pago ***

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CONSIGNACION	BANCO DE BOGOTA	062754387	392360441	25/01/2011	571.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	571.000.00	571.000.00
				$571.000.00

SON: **QUINIENTOS SETENTA Y UN MIL PESOS MONEDA CORRIENTE***

Responsable: _____

-*-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-008053- -00000-0000
Fecha: 2011-01-25 17:07:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 334

TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS

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 Minjusticia

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.

Traductor: Jorge Enrique Sierra Reyes.

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Licencia 376 - 1993 Minjusticia

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OLARTE RAISBECK & FRIERI LTDA.

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José Luis Londoño
Felipe Mendoza
Simón Salinas

Of Counsel
Guillermo Chahin
Graciela Melo

33842-CO-PCT

Power of Attorney

The undersigned,

domiciled in

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

Poder

El suscrito,

IRM LLC, a Delaware Limited Liability Company

domiciliado en

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

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, Note

Leg.Prot.Nr. 1591 /2006

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Confédération Suisse)
This official document
2. is signed by
3. in his/her function
4. and certified
Certified 20. NOV. 2006
5. in Basel (Bâle) 6. on
7. by the State Chancery of the Canton of Basel-Stadt
8. No 2006/1728
9. Seal/stamp: 10. Signature:
Heidi Fischer

STATE CHANCERY * BASLE-CITY

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

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(75) Inventors/Applicants *(for US only)*: **MARSILJE III, Thomas H.** [US/US]; 1844 Narragansett Court, San Diego, California 92107 (US). **LU, Wenshuo** [CA/US]; 7594 Wallingford Court, San Diego, California 92126 (US). **CHEN, Bei** [CN/US]; 11048 Creekbridge Place, San Diego, California 92128 (US). **HE, Xiaohui** [CN/US]; 12461 Dornouse Road, San Diego, California 92129 (US). **LEE, Christian Cho-Hua** [US/US]; 11115 Ice Skate Place, San Diego, California 92126 (US). **JIANG, Songchun** [CN/US]; 10512 Rancho Carmel Drive, San Diego, California 92128 (US). **YANG, Kunyong** [CN/US]; 11861 Spruce Run Drive, #C, San Diego, California 92131 (US).

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, 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, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

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

WO 2010/002655 A2

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

(57) **Abstract**: The invention provides novel pyrimidine derivatives and pharmaceutical compositions thereof, and methods for using such compounds. For example, the pyrimidine derivatives of the invention may be used to treat, ameliorate or prevent a condition which responds to inhibition of insulin-like growth factor (IGF-1R) or analplastic lymphoma kinase (ALK).

COMPOUNDS AND COMPOSITIONS AS KINASE INHIBITORS

Cross-Reference to Related Applications

[0001] This application claims the benefit of U.S. provisional application serial numbers 61/075,583, filed 25 June 2008, and 61/155,434, filed 25 February 2009, each of which is incorporated herein by reference in its entirety.

Technical Field

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

Background Art

[0003] 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)).

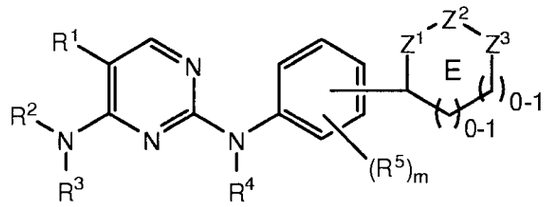
[0004] Anaplastic lymphoma kinase (ALK), a member of the insulin receptor superfamily of receptor tyrosine kinases, has been implicated in oncogenesis in hematopoietic and non-hematopoietic tumors. The aberrant expression of full-length ALK receptor proteins has been reported in neuroblastomas and glioblastomas; 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)).

[0005] Because of the emerging disease-related roles of IGF-1R and ALK, there is a continuing need for compounds which may be useful for treating and preventing a disease which responds to inhibition of IGF-1R and ALK.

Disclosure of the Invention

[0006] The invention relates to novel pyrimidine derivatives and pharmaceutical compositions thereof, and their use as pharmaceuticals.

[0007] In one aspect, the invention provides a compound of Formula (1):



(1)

or a physiologically acceptable salt thereof;

wherein ring E may optionally contain a double bond;

one of Z^1, Z^2 and Z^3 is NR^6, $N(R^6)^+$-O^- or $S(O)_{1-2}$ and the others are CR_2;

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

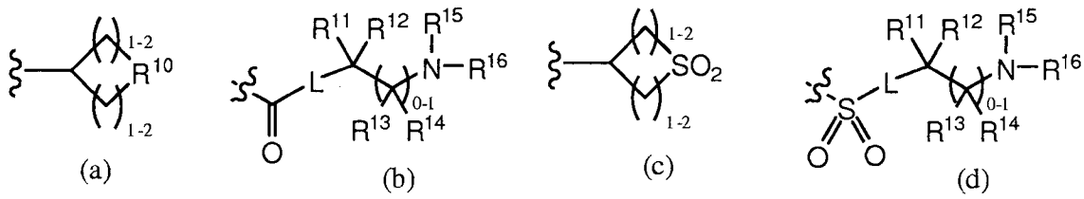
R^2 is pyridine-2-onyl, azepan-2-onyl or a monocyclic 5-6 membered heteroaryl having 1-3 heteroatoms selected from N, O and S; each of which is optionally substituted substituted with R^9 wherein R^9 is C_{1-6} alkyl, C_{1-6} haloalkyl or C_{3-7} cycloalkyl;

R^3 and R^4 are each H;

R^5 is halo, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted C_{1-6} alkyl, halo-substituted C_{1-6} alkoxy, cyano or $C(O)O_{0-1}R^8$;

R^6 is H; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo and/or hydroxyl groups; -$(CR_2)_p$-OR^7, -$(CR_2)_p$-$CH(OH)C_tF_{2t+1}$ wherein t is 1-3, $(CR_2)_p$-CN; $(CR_2)_p$-$NR(R^7)$, -$(CR_2)_p$–$C(O)OR^7$, $(CR_2)_pNR(CR_2)_pOR^7$,
$(CR_2)_pNR$-L-$C(O)R^8$, $C(O)(CR_2)_qOR^8$, -$C(O)O$-$(CR_2)_p$-NRR^7, –C(O) -$(CR_2)_p$-OR^7, L-Y,
-L-$C(O)R^7$, -L–C(O)-NRR^7, -L–C(O)-NR-$(CR_2)_p$-NRR^7,-L-$C(O)NR(CR_2)_pOR^7$,
-L–C(O)-$(CR_2)_q$-NR-C(O)-R^8, -L-$C(O)NR(CR_2)_pSR^7$, -L-$C(O)NR(CR_2)_pS(O)_{1-2}R^8$,
-L-$S(O)_2R^8$, -L-$S(O)_2$-$(CR_2)_q$-NRR^7, -L-$S(O)_2NR(CR_2)_pNR(R^7)$ or
-L-$S(O)_2NR(CR_2)_pOR^7$;

alternatively, R^6 is a radical selected from formula (a), (b), (c) or (d):



(a) (b) (c) (d)

R^{10} is O, S, NR^{17} wherein R^{17} is H, C_{1-6} alkyl, SO_2R^{8a} or CO_2R^{8a};

R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are independently selected from H; C_{1-6} alkoxy; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino or hydroxyl groups; or R^{11} and R^{12}, R^{12} and R^{15}, R^{15} and R^{16}, R^{13} and R^{14}, or R^{13} and R^{15} together with the atoms to which they are attached may form a 3-7 membered saturated, unsaturated or partially unsaturated ring containing 1-3 heteroatoms selected from N, O and S, and optionally substituted with oxo and 1-3 R^5 groups;

L is $(CR_2)_{1-4}$ or a bond;

Y is C_{3-7} carbocyclic ring, C_{6-10} aryl, or a 5-10 membered heteroaryl or 4-10 membered heterocyclic ring, each of which is optionally substituted with 1-3 R^5 groups;

R^7, R^8 and R^{8a} are independently C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino, hydroxyl or cyano; $(CR_2)_qY$ or C_{1-6} alkoxy; or R^7 is H;

each R is independently H or C_{1-6} alkyl;

R and R^7 together with N in each NRR^7 may form a 5-6 membered ring containing 1-3 heteroatoms selected from N, O and S, and optionally substituted with oxo and 1-3 R^5 groups;

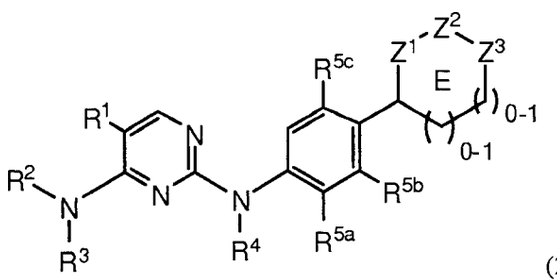
m is 2-4;

n is 1-3;

p is 1-4; and

q is 0-4.

[0008] In one embodiment, the invention provides a compound is of Formula (2):



(2)

wherein one of R^{5a}, R^{5b} and R^{5c} is H and the others are independently halo, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted C_{1-6} alkyl, cyano or $C(O)O_{0-1}R^8$ wherein R^8 is C_{1-6} alkyl; and

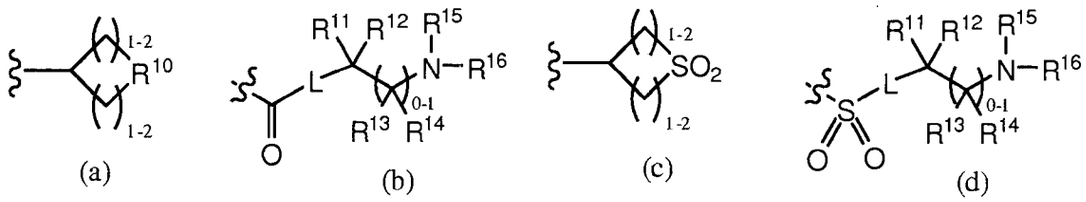
R^1, R^2, R^3, R^4, E, Z^1, Z^2 and Z^3 are as defined in Formula (1).

[0009] In some examples, Z^3 in the above Formula (2) is NR^6 or $N(R^6)^+$-O^-; and Z^1 and Z^2 are CH_2. In other examples, R^6 is H, C_{1-6} alkyl optionally substituted with halo and/or hydroxyl groups; -$(CR_2)_p$-OR^7, -$(CR_2)_p$-$CH(OH)C_tF_{2t+1}$ wherein t is 1-3, L-Y,

$(CR_2)_p$-CN; $(CR_2)_p$-$NR(R^7)$, -$(CR_2)_p$–$C(O)OR^7$, $C(O)(CR_2)_qOR^8$, -C(O)O-$(CR_2)_p$-NRR^7,

-L-$C(O)R^7$, -L–C(O)-NRR^7, -L–C(O)-NR-$(CR_2)_p$-NRR^7, -L–C(O)-$(CR_2)_q$-NR-C(O)-R^8,

-L-$S(O)_2R^8$, -L-$S(O)_2$-$(CR_2)_q$-NRR^7, or a radical selected from formula (a), (b), (c) or (d):



(a) (b) (c) (d)

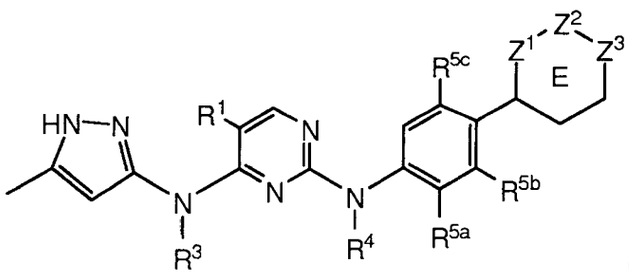
R^{10} is O, S, NR^{17} wherein R^{17} is H, C_{1-6} alkyl, SO_2R^{8a} or CO_2R^{8a};

R^{8a} is C_{1-6} alkyl; and

R^7, R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R, L, Y, p and q are as defined in Formula (1).

[0010] In the above Formula (1) and (2), R^2 may be pyrazolyl, isoxazolyl, pyridine-2-onyl or azepan-2-onyl, each of which is substituted with C_{1-6} alkyl, C_{1-6} haloalkyl or C_{3-7} cycloalkyl.

[0011] In another embodiment, the invention provides a compound of Formula (3):



(3)

or a tautomer thereof;

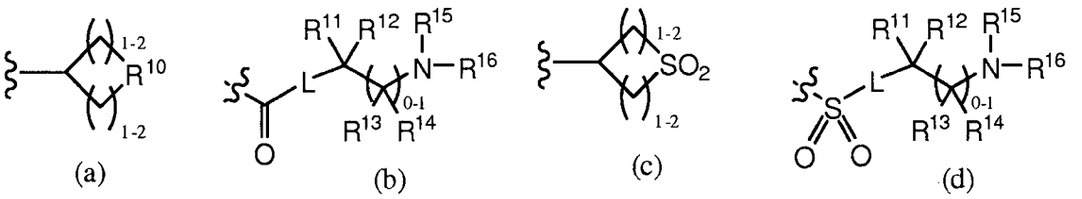
wherein R^{5b} is H; and R^{5a} and R^{5c} are independently halo, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted C_{1-6} alkyl, cyano or $C(O)O_{0-1}R^8$ wherein R^8 is C_{1-6} alkyl;

Z^1 and Z^2 are CH^2;

Z^3 is NR^6 or $N(R^6)^+$-O^-;

R^6 is H, C_{1-6} alkyl optionally substituted with halo and/or hydroxyl groups; -$(CR_2)_p$-OR^7, -$(CR_2)_p$-$CH(OH)C_tF_{2t+1}$ wherein t is 1-3, $(CR_2)_p$-CN; $(CR_2)_p$-$NR(R^7)$, -$(CR_2)_p$–$C(O)OR^7$, $C(O)(CR_2)_qOR^8$, -$C(O)O$-$(CR_2)_p$-NRR^7, L-Y, -L-$C(O)R^7$, -L–$C(O)$-NRR^7, -L–$C(O)$-NR-$(CR_2)_p$-NRR^7, -L–$C(O)$-$(CR_2)_q$-NR-$C(O)$-R^8, -L-$S(O)_2R^8$,

-L-$S(O)_2$-$(CR_2)_q$-NRR^7, or a radical selected from formula (a), (b), (c) or (d):



(a) (b) (c) (d)

R^{10} is O, S, NR^{17} wherein R^{17} is H, C_{1-6} alkyl, SO_2R^{8a} or CO_2R^{8a};

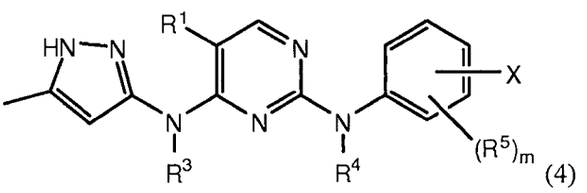
R^{8a} is C_{1-6} alkyl; and

R^1, R^3, R^4, R^7, R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R, L, Y, p, q and E are as defined in Formula (1).

[0012] In the above Formula (3), R^{5a} may be halo and R^{5c} is C_{1-6} alkyl. In some examples, R^6 is C_{1-6} alkyl or a a radical of formula (a) or (c); and R^{10} is O.

[0013] In the above Formula (1), (2) and (3), R^1 may be halo. In particular examples, R^1 is chloro. In other examples, R^3 and R^4 are H.

[0014] In another aspect, the present invention provides a compound of Formula (4):



(4)

or a physiologically acceptable salt thereof;

wherein X is a monocyclic 5-6 membered heterocyclic ring containing 1-3 heteroatoms selected from N, O and S, and optionally substituted on a substitutable ring carbon with oxo and at any substitutable ring nitrogen by R^6;

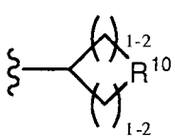
R^1 is halo;

R^3 and R^4 are each H;

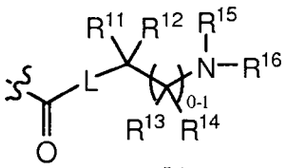
R^5 is halo, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted C_{1-6} alkyl, halo-substituted C_{1-6} alkoxy, cyano or $C(O)O_{0-1}R^8$;

R^6 is H; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo and/or hydroxyl groups; $-(CR_2)_p-OR^7$, $-(CR_2)_p-CH(OH)C_tF_{2t+1}$ wherein t is 1-3, $(CR_2)_p-CN$; $(CR_2)_p-NR(R^7)$, $-(CR_2)_p-C(O)OR^7$, $(CR_2)_pNR(CR_2)_pOR^7$, $(CR_2)_pNR-L-C(O)R^8$, $C(O)(CR_2)_qOR^8$, $-C(O)O-(CR_2)_p-NRR^7$, $-C(O)-(CR_2)_p-OR^7$, L-Y, $-L-C(O)R^7$, $-L-C(O)-NRR^7$, $-L-C(O)-NR-(CR_2)_p-NRR^7$, $-L-C(O)NR(CR_2)_pOR^7$, $-L-C(O)-(CR_2)_q-NR-C(O)-R^8$, $-L-C(O)NR(CR_2)_pSR^7$, $-L-C(O)NR(CR_2)_pS(O)_{1-2}R^8$, $-L-S(O)_2R^8$, $-L-S(O)_2-(CR_2)_q-NRR^7$, $-L-S(O)_2NR(CR_2)_pNR(R^7)$ or $-L-S(O)_2NR(CR_2)_pOR^7$;

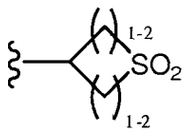
alternatively, R^6 is a radical selected from formula (a), (b), (c) or (d):



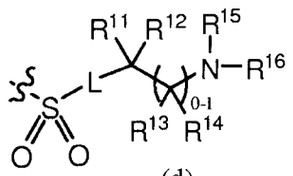
(a)



(b)



(c)



(d)

R^{10} is O, S, NR^{17} wherein R^{17} is H, C_{1-6} alkyl, SO_2R^{8a} or CO_2R^{8a};

R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are independently selected from H; C_{1-6} alkoxy; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino or hydroxyl groups; or R^{11} and R^{12}, R^{12} and R^{15}, R^{15} and R^{16}, R^{13} and R^{14}, or R^{13} and R^{15} together with the atoms to which they are attached may form a 3-7 membered saturated, unsaturated or partially unsaturated ring containing 1-3 heteroatoms selected from N, O and S, and optionally substituted with oxo and 1-3 R^5 groups;

L is $(CR_2)_{1-4}$ or a bond;

Y is C_{3-7} carbocyclic ring, C_{6-10} aryl, or a 5-10 membered heteroaryl or 4-10 membered heterocyclic ring, each of which is optionally substituted with 1-3 R^5 groups;

R^7, R^8 and R^{8a} are independently C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino, hydroxyl or cyano; $(CR_2)_qY$ or C_{1-6} alkoxy; or R^7 is H;

each R is independently H or C_{1-6} alkyl;

R and R^7 together with N in each NRR^7 may form a 5-6 membered ring containing 1-3 heteroatoms selected from N, O and S, and optionally substituted with oxo and 1-3 R^5 groups;

m is 2-4;

n is 1-3;

p is 1-4; and

q is 0-4.

[0015] In the above Formula (4), X may be morpholinyl, piperazinyl, piperazin-2-onyl, oxazolidin-2-onyl or piperidin-2-onyl each of which is substituted at any substitutable ring nitrogen by C_{1-6} alkyl; or X is tetrahydro-2H-pyran-2-onyl; and R^1 is chloro.

[0016] In another aspect, the present invention provides pharmaceutical compositions comprising a compound having Formula (1), (2), (3) and (4), and a physiologically acceptable excipient.

[0017] In yet another aspect, the invention provides methods for inhibiting IGF-1R in a cell, comprising contacting the cell with an effective amount of a compound having Formula (1), (2), (3) and (4) or a pharmaceutical composition thereof.

[0018] The invention also provides methods to treat, ameliorate or prevent a condition which responds to inhibition of IGF-1R or anaplastic lymphoma kinase (ALK) in a mammal suffering from said condition, comprising administering to the mammal a therapeutically effective amount of a compound having Formula (1), (2), (3) and (4) or a pharmaceutical composition thereof, and optionally in combination with a second therapeutic agent. Alternatively, the present invention provides for the use of a compound having Formula (1), (2), (3) and (4), and optionally in combination with a second therapeutic agent, in the manufacture of a medicament for treating a condition mediated by IGF-1R or ALK. The compounds of the invention may be administered, for example, to a mammal suffering from an autoimmune disease, a transplantation disease, an infectious disease or 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, multiple myeloma, neuroblastoma, synovial, hepatocellular, Ewing's Sarcoma or a solid tumor selected from a osteosarcoma,

melanoma, and tumor of breast, renal, prostate, colorectal, thyroid, ovarian, pancreatic, lung, uterine or gastrointestinal tumor.

Definitions

[0019] "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).

[0020] "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.

[0021] "Heteroaryl" as used herein is as defined for aryl above, where one or more of the ring members is a heteroatom. For example, a heteroaryl substituent for use in the compounds of the invention may be a monocyclic or bicyclic 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S. 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.

[0022] 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.

[0023] 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 for use in the compounds of the invention may be a 4-7 membered heterocyclic ring containing 1-3 heteroatoms selected from N, O and S, or a combination thereof

such as -S(O) or -$S(O)_2$-. Examples of heterocyclic rings include but are not limited to azetidinyl, 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.

[0024] As used herein, an H atom in any substituent groups (e.g., CH_2) encompasses all suitable isotopic variations, e.g., H, ^2H and ^3H.

[0025] 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.

[0026] "Mammal" refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. In particular examples, the mammal is human.

[0027] 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. Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order, and in any route of administration.

[0028] An "effective amount" of a compound is an amount sufficient to carry out a specifically stated purpose. An "effective amount" may be determined empirically and in a routine manner, in relation to the stated purpose.

[0029] The term "therapeutically effective amount" refers to an amount of a compound (e.g., an IGF-1R antagonist) effective to "treat" an IGF-1R-mediated disorder in a subject or mammal. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size;

inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. See the definition herein of "treating". To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic.

[0030] The term "cancer" refers to the physiological condition in mammals that is typically characterized by unregulated cell growth/proliferation. Examples of cancer include, but are not limited to: carcinoma, lymphoma, blastoma, and leukemia. More particular examples of cancers include, but are not limited to: chronic lymphocytic leukemia (CLL), lung, including non small cell (NSCLC), breast, ovarian, cervical, endometrial, prostate, colorectal, intestinal carcinoid, bladder, gastric, pancreatic, hepatic (hepatocellular), hepatoblastoma, esophageal, pulmonary adenocarcinoma, mesothelioma, synovial sarcoma, osteosarcoma, head and neck squamous cell carcinoma, juvenile nasopharyngeal angiofibromas, liposarcoma, thyroid, melanoma, basal cell carcinoma (BCC), medulloblastoma and desmoid.

[0031] "Treating" or "treatment" or "alleviation" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic disease or condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to having the disorder or those in whom the disorder is to be prevented (prophylaxis). When the IGF-1R-mediated disorder is cancer, a subject or mammal is successfully "treated" or shows a reduced tumor burden if, after receiving a therapeutic amount of an IGF-1R antagonist according to the methods of the present invention, the patient shows observable and/or measurable reduction in or absence of one or more of the following: reduction in the number of cancer cells or absence of the cancer cells; reduction in the tumor size; inhibition (i.e., slow to some extent and preferably stop) of cancer cell infiltration into peripheral organs including the spread of cancer into soft tissue and bone; inhibition (i.e., slow to some extent and preferably stop) of tumor metastasis; inhibition, to some extent, of tumor growth; and/or relief to some extent, one or more of the symptoms associated with the specific cancer; reduced morbidity and mortality, and improvement in quality of life issues. To the extent the IGF-1R antagonist may prevent growth and/or kill existing cancer cells, it may be cytostatic

and/or cytotoxic. Reduction of these signs or symptoms may also be felt by the patient.

[0032] "Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN®, polyethylene glycol (PEG), and PLURONICS®.

[0033] A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include alkylating agents such as thiotepa and CYTOXAN® cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); delta-9-tetrahydrocannabinol (dronabinol, MARINOL®); beta-lapachone; lapachol; colchicines; betulinic acid; a camptothecin (including the synthetic analogue topotecan (HYCAMTIN®), CPT-11 (irinotecan, CAMPTOSAR®), acetylcamptothecin, scopolectin, and 9-aminocamptothecin); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); podophyllotoxin; podophyllinic acid; teniposide; cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine,

trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gamma1I and calicheamicin omegaI1 (see, e.g., Agnew, Chem Intl. Ed. Engl., 33: 183-186 (1994)); dynemicin, including dynemicin A; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2′,2″-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine (ELDISINE®, FILDESIN®); dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); thiotepa; taxoids, e.g., TAXOL® paclitaxel (Bristol-Myers Squibb Oncology, Princeton, N.J.), ABRAXANE™ Cremophor-free,

albumin-engineered nanoparticle formulation of paclitaxel (American Pharmaceutical Partners, Schaumberg, Ill.), and TAXOTERE® doxetaxel (Rhône-Poulenc Rorer, Antony, France); chloranbucil; gemcitabine (GEMZAR®); 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine (VELBAN®); platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine (ONCOVIN®); oxaliplatin; leucovovin; vinorelbine (NAVELBINE®); novantrone; edatrexate; daunomycin; aminopterin; ibandronate; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine (XELODA®); pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above such as CHOP, an abbreviation for a combined therapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone, and FOLFOX, an abbreviation for a treatment regimen with oxaliplatin (ELOXATIN™) combined with 5-FU and leucovovin.

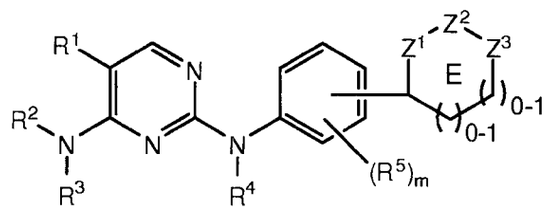
[0034] Furthermore, a "chemotherapeutic agent" may include anti-hormonal agents that act to regulate, reduce, block, or inhibit the effects of hormones that can promote the growth of cancer, and are often in the form of systemic, or whole-body treatment. They may be hormones themselves. Examples include anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX® tamoxifen), EVISTA® raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON® toremifene; anti-progesterones; estrogen receptor down-regulators (ERDs); agents that function to suppress or shut down the ovaries, for example, leutinizing hormone-releasing hormone (LHRH) agonists such as LUPRON® and ELIGARD® leuprolide acetate, goserelin acetate, buserelin acetate and tripterelin; other anti-androgens such as flutamide, nilutamide and bicalutamide; and aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® megestrol acetate, AROMASIN® exemestane, formestanie, fadrozole, RIVISOR® vorozole, FEMARA® letrozole, and ARIMIDEX® anastrozole. In addition, such definition of chemotherapeutic agents includes bisphosphonates such as clodronate (for example, BONEFOS® or OSTAC®), DIDROCAL® etidronate, NE-58095, ZOMETA® zoledronic acid/zoledronate, FOSAMAX® alendronate, AREDIA® pamidronate, SKELID® tiludronate, or ACTONEL® risedronate; as well as troxacitabine (a 1,3-

dioxolane nucleoside cytosine analog); antisense oligonucleotides, particularly those that inhibit expression of genes in signaling pathways implicated in abherant cell proliferation, such as, for example, PKC-alpha, Raf, H-Ras, and epidermal growth factor receptor (EGF-R); vaccines such as THERATOPE® vaccine and gene therapy vaccines, for example, ALLOVECTIN® vaccine, LEUVECTIN® vaccine, and VAXID® vaccine; LURTOTECAN® topoisomerase 1 inhibitor; ABARELIX® rmRH; lapatinib ditosylate (an ErbB-2 and EGFR dual tyrosine kinase small-molecule inhibitor also known as GW572016); and pharmaceutically acceptable salts, acids or derivatives of any of the above.

Modes of Carrying Out the Invention

[0035] The invention provides novel pyrimidine derivatives and pharmaceutical compositions thereof, and methods for using such compounds.

[0036] In one aspect, the invention provides a compound of Formula (1):



(1)

or a physiologically acceptable salt thereof;

wherein ring E may optionally contain a double bond;

one of Z^1, Z^2 and Z^3 is NR^6, $N(R^6)^+$-O^- or $S(O)_{1-2}$ and the others are CR_2;

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

R^2 is pyridine-2-onyl, azepan-2-onyl or a monocyclic 5-6 membered heteroaryl having 1-3 heteroatoms selected from N, O and S; each of which is optionally substituted substituted with R^9 wherein R^9 is C_{1-6} alkyl, C_{1-6} haloalkyl or C_{3-7} cycloalkyl;

R^3 and R^4 are each H;

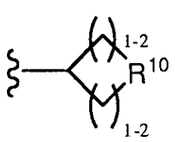
R^5 is halo, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted C_{1-6} alkyl, halo-substituted C_{1-6} alkoxy, cyano or $C(O)O_{0-1}R^8$;

R^6 is H; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo and/or hydroxyl groups; $-(CR_2)_p-OR^7$, $-(CR_2)_p-CH(OH)C_tF_{2t+1}$ wherein t is 1-3, $(CR_2)_p-CN$; $(CR_2)_p-NR(R^7)$, $-(CR_2)_p-C(O)OR^7$, $(CR_2)_pNR(CR_2)_pOR^7$,

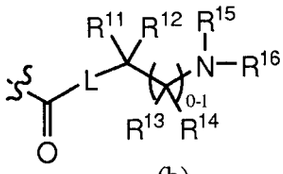
$(CR_2)_pNR$-L-$C(O)R^8$, $C(O)(CR_2)_qOR^8$, $-C(O)O-(CR_2)_p-NRR^7$, $-C(O)-(CR_2)_p-OR^7$, L-Y,

$-L-C(O)R^7$, $-L-C(O)-NRR^7$, $-L-C(O)-NR-(CR_2)_p-NRR^7$, $-L-C(O)NR(CR_2)_pOR^7$, $-L-C(O)-(CR_2)_q-NR-C(O)-R^8$, $-L-C(O)NR(CR_2)_pSR^7$, $-L-C(O)NR(CR_2)_pS(O)_{1-2}R^8$, $-L-S(O)_2R^8$, $-L-S(O)_2-(CR_2)_q-NRR^7$, $-L-S(O)_2NR(CR_2)_pNR(R^7)$ or $-L-S(O)_2NR(CR_2)_pOR^7$;

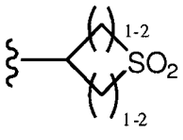
alternatively, R^6 is a radical selected from formula (a), (b), (c) or (d):



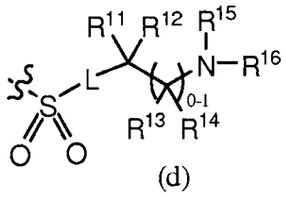
(a)



(b)



(c)



(d)

R^{10} is O, S, NR^{17} wherein R^{17} is H, C_{1-6} alkyl, SO_2R^{8a} or CO_2R^{8a};

R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are independently selected from H; C_{1-6} alkoxy; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino or hydroxyl groups; or R^{11} and R^{12}, R^{12} and R^{15}, R^{15} and R^{16}, R^{13} and R^{14}, or R^{13} and R^{15} together with the atoms to which they are attached may form a 3-7 membered saturated, unsaturated or partially unsaturated ring containing 1-3 heteroatoms selected from N, O and S, and optionally substituted with oxo and 1-3 R^5 groups;

L is $(CR_2)_{1-4}$ or a bond;

Y is C_{3-7} carbocyclic ring, C_{6-10} aryl, or a 5-10 membered heteroaryl or 4-10 membered heterocyclic ring, each of which is optionally substituted with 1-3 R^5 groups;

R^7, R^8 and R^{8a} are independently C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino, hydroxyl or cyano; $(CR_2)_qY$ or C_{1-6} alkoxy; or R^7 is H;

each R is independently H or C_{1-6} alkyl;

R and R^7 together with N in each NRR^7 may form a 5-6 membered ring containing 1-3 heteroatoms selected from N, O and S, and optionally substituted with oxo and 1-3 R^5 groups;

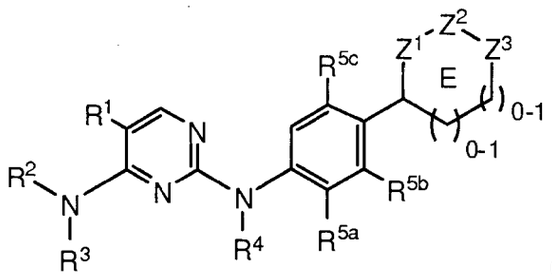
m is 2-4;

n is 1-3;

p is 1-4; and

q is 0-4.

[0037] In one embodiment, the invention provides a compound is of Formula (2):

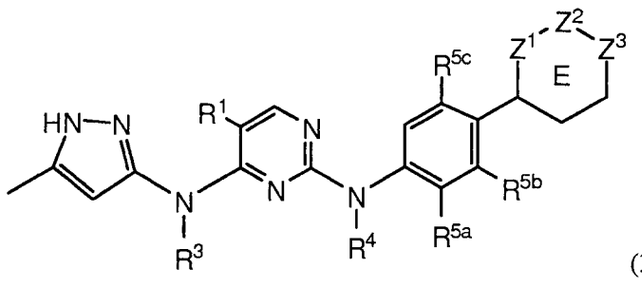


(2)

wherein one of R^{5a}, R^{5b} and R^{5c} is H and the others are independently halo, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted C_{1-6} alkyl, cyano or $C(O)O_{0-1}R^8$ wherein R^8 is C_{1-6} alkyl; and

R^1, R^2, R^3, R^4, E, Z^1, Z^2 and Z^3 are as defined in Formula (1).

[0038] In another embodiment, the invention provides a compound of Formula (3):



(3)

or a tautomer thereof;

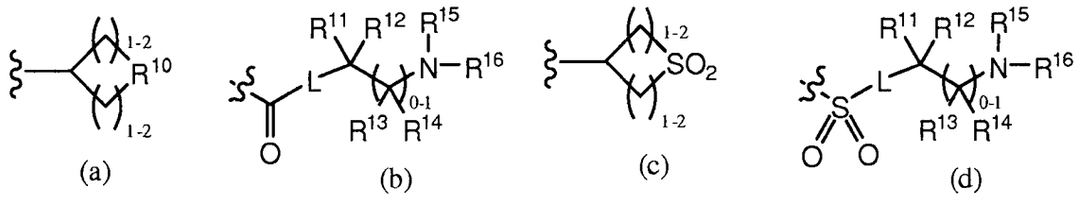
wherein R^{5b} is H; and R^{5a} and R^{5c} are independently halo, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted C_{1-6} alkyl, cyano or $C(O)O_{0-1}R^8$ wherein R^8 is C_{1-6} alkyl;

Z^1 and Z^2 are CH^2;

Z^3 is NR^6 or $N(R^6)^+$-O^-;

R^6 is H, C_{1-6} alkyl optionally substituted with halo and/or hydroxyl groups; -$(CR_2)_p$-OR^7, -$(CR_2)_p$-$CH(OH)C_tF_{2t+1}$ wherein t is 1-3, $(CR_2)_p$-CN; $(CR_2)_p$-$NR(R^7)$, -$(CR_2)_p$–$C(O)OR^7$, $C(O)(CR_2)_qOR^8$, -$C(O)O$-$(CR_2)_p$-NRR^7, L-Y, -L-$C(O)R^7$, -L–C(O)-NRR^7, -L–C(O)-NR-$(CR_2)_p$-NRR^7, -L–C(O)-$(CR_2)_q$-NR-C(O)-R^8, -L-$S(O)_2R^8$,

-L-$S(O)_2$-$(CR_2)_q$-NRR^7, or a radical selected from formula (a), (b), (c) or (d):



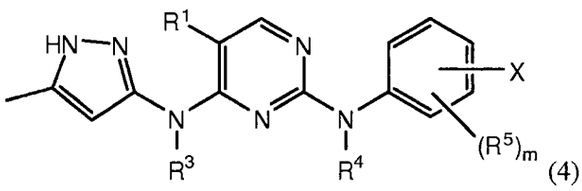
(a) (b) (c) (d)

R^{10} is O, S, NR^{17} wherein R^{17} is H, C_{1-6} alkyl, SO_2R^{8a} or CO_2R^{8a};

R^{8a} is C_{1-6} alkyl; and

R^1, R^3, R^4, R^7, R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R, L, Y, p, q and E are as defined in Formula (1).

[0039] In another aspect, the present invention provides a compound of Formula (4):



(4)

or a physiologically acceptable salt thereof;

wherein X is a monocyclic 5-6 membered heterocyclic ring containing 1-3 heteroatoms selected from N, O and S, and optionally substituted on a substitutable ring carbon with oxo and at any substitutable ring nitrogen by R^6;

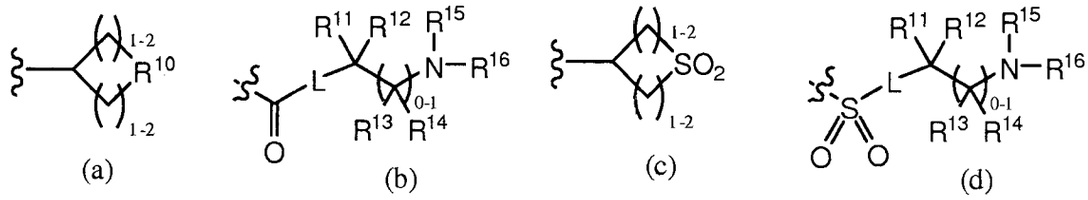
R^1 is halo;

R^3 and R^4 are each H;

R^5 is halo, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted C_{1-6} alkyl, halo-substituted C_{1-6} alkoxy, cyano or $C(O)O_{0-1}R^8$;

R^6 is H; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo and/or hydroxyl groups; $-(CR_2)_p-OR^7$, $-(CR_2)_p-CH(OH)C_tF_{2t+1}$ wherein t is 1-3, $(CR_2)_p-CN$; $(CR_2)_p-NR(R^7)$, $-(CR_2)_p–C(O)OR^7$, $(CR_2)_pNR(CR_2)_pOR^7$, $(CR_2)_pNR-L-C(O)R^8$, $C(O)(CR_2)_qOR^8$, $-C(O)O-(CR_2)_p-NRR^7$, $–C(O)-(CR_2)_p-OR^7$, L-Y, $-L-C(O)R^7$, $-L–C(O)-NRR^7$, $-L–C(O)-NR-(CR_2)_p-NRR^7$, $-L-C(O)NR(CR_2)_pOR^7$, $-L–C(O)-(CR_2)_q-NR-C(O)-R^8$, $-L-C(O)NR(CR_2)_pSR^7$, $-L-C(O)NR(CR_2)_pS(O)_{1-2}R^8$, $-L-S(O)_2R^8$, $-L-S(O)_2-(CR_2)_q-NRR^7$, $-L-S(O)_2NR(CR_2)_pNR(R^7)$ or $-L-S(O)_2NR(CR_2)_pOR^7$;

alternatively, R^6 is a radical selected from formula (a), (b), (c) or (d):



(a) (b) (c) (d)

R^{10} is O, S, NR^{17} wherein R^{17} is H, C_{1-6} alkyl, SO_2R^{8a} or CO_2R^{8a};

R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are independently selected from H; C_{1-6} alkoxy; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino or hydroxyl groups; or R^{11} and R^{12}, R^{12} and R^{15}, R^{15} and R^{16}, R^{13} and R^{14}, or R^{13} and R^{15} together with the atoms to which they are attached may form a 3-7 membered saturated, unsaturated or partially unsaturated ring containing 1-3 heteroatoms selected from N, O and S, and optionally substituted with oxo and 1-3 R^5 groups;

L is $(CR_2)_{1-4}$ or a bond;

Y is C_{3-7} carbocyclic ring, C_{6-10} aryl, or a 5-10 membered heteroaryl or 4-10 membered heterocyclic ring, each of which is optionally substituted with 1-3 R^5 groups;

R^7, R^8 and R^{8a} are independently C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino, hydroxyl or cyano; $(CR_2)_qY$ or C_{1-6} alkoxy; or R^7 is H;

each R is independently H or C_{1-6} alkyl;

R and R^7 together with N in each NRR^7 may form a 5-6 membered ring containing 1-3 heteroatoms selected from N, O and S, and optionally substituted with oxo and 1-3 R^5 groups;

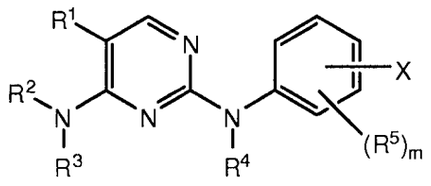
m is 2-4;

n is 1-3;

p is 1-4; and

q is 0-4.

[0040] In yet another aspect, the invention provides compounds of Formula (5):


(1)

or physiologically acceptable salts thereof;

wherein X is a 4-7 membered heterocyclic ring containing NR^6, $-\overset{O^-}{\underset{|}{N^+}}R^6$, O or S, and optionally substituted with 1-3 R^5 groups;

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

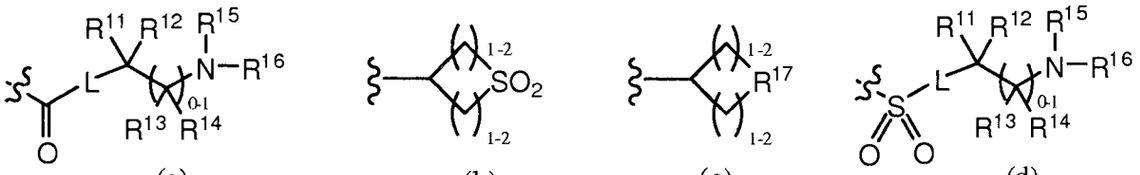
R^2 is an optionally substituted 5-6 membered heteroaryl or 5-7 membered heterocyclic ring, each having 1-3 heteroatoms selected from N, O and S and optionally substituted with 1-3 R^9 groups;

R^3 and R^4 are independently H, $C(O)R^8$, C_{1-6} alkyl or halo-substituted C_{1-6} alkyl;

R^5 and R^9 are independently C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino or hydroxyl groups; or R^5 and R^9 are independently C_{1-6} alkoxy, halo-substituted C_{1-6} alkoxy, halo, nitro, cyano, $CR(OR^7)R^7$, OR^7, $O(CR_2)_p$-OR^7, $NR(R^7)$, $CR(R^7)NRR^7$, $(CR_2)_{1-6}NR(CR_2)_pOR^7$, $(CR_2)_{1-6}NR(CR_2)_qC(O)R^8$, $-C(O)$-$(CR_2)_q$-NR-$C(O)$-R^8, $(CR_2)_qY$, $C(O)O_{0-1}R^7$, $C(O)NR(R^7)$, $C(O)CRR^7$-$NR(R^7)$, $C(O)NR(CR_2)_pNR(R^7)$, $C(O)NR(CR_2)_pOR^7$, $C(O)NR(CR_2)_pSR^7$, $C(O)NR(CR_2)_pS(O)_{1-2}R^8$, $S(O)_{0-2}R^8$, $S(O)_2NRR^7$, $S(O)_2NR(CR_2)_pNR(R^7)$, or $S(O)_2NR(CR_2)_pOR^7$;

R^6 is H; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino, hydroxyl or alkoxy; $-(CR_2)_p$-CN; C(O)H, $CR(OR^7)R^7$, $(CR_2)_p$-OR^7, $(CR_2)_p$-$NR(R^7)$, $CR(R^7)NRR^7$, -L-Y, -L–$C(O)O_{0-1}$-$(CR_2)_q$-R^8, -$(CR_2)_p$–$C(O)O_{0-1}$-R^7, -L–C(O)-NRR^7, -L–$C(O)O_{0-1}$-$CR(R^7)$-NRR^7, -L–C(O)-NR-$(CR_2)_p$-NRR^7, -L-$C(O)NR(CR_2)_pOR^7$, -L–C(O)-$(CR_2)_q$-NR-$C(O)$-R^8, -L-$C(O)NR(CR_2)_pSR^7$, -L-$C(O)NR(CR_2)_pS(O)_{1-2}R^8$, -L-$S(O)_2R^8$, $(CR_2)_pNR(CR_2)_pOR^7$, $(CR_2)_pNR$-L-$C(O)R^8$, -L-$S(O)_2NRR^7$, -L-$S(O)_2NR(CR_2)_pNR(R^7)$ or -L-$S(O)_2NR(CR_2)_pOR^7$;

alternatively, R^6 is a radical selected from formula (a), (b), (c) or (d):



(a) (b) (c) (d)

wherein R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are independently selected from H or C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino or hydroxyl groups; or R^{11} and R^{12}, R^{12} and R^{15}, R^{15} and R^{16}, R^{13} and R^{14}, or R^{13} and R^{15} together with the carbon and/or nitrogen atoms to which they are attached may form a 3-7 membered saturated, unsaturated or partially unsaturated ring optionally containing up to 3 atoms or groups selected from C(O), N, O and $S(O)_{0-2}$;

R^{17} is O or SO_2R^8;

L is $(CR_2)_{1-4}$ or a bond;

Y is C_{3-7} carbocyclic ring, C_{6-10} aryl, or a 5-10 membered heteroaryl or 4-10 membered heterocyclic ring, each of which is optionally substituted with 1-3 R^5 groups;

R^7 and R^8 are independently C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino, hydroxyl or cyano; $(CR_2)_qY$ or C_{1-6} alkoxy; or R^7 is H;

each R is H or C_{1-6} alkyl;

m is 2-4;

n is 1-3;

p is 1-4; and

q is 0-4.

[0041] In the above Formula (5), examples of 5-6 membered heteroaryl or 5-7 membered heterocyclic ring R^2 groups include but are not limited to pyrazolyl, pyrrolyl, thiophenyl, pyrimidinyl, isoxazolyl, pyridyl, azepan-2-onyl, 2H-thipyran, 3H- thipyran, 4H-thipyran, tetrahydrothiopyran, 2H-pyran, 4H-pyran, tetrahydropyran, piperidine, 1,2-dithiin, 1,2-dithiane, 1,3-dithiin, 1, 3-dithiane, 1,4-dithiin, 1,4-dithiane, 1,2- dioxin, 1,2-dioxane, 1,3-dioxin, 1,3-dioxane, 1,4-dioxin, 1,4-dioxane, piperazine, 1,2- oxathiin, 1,2-oxathiane, 4H-1, 3-oxathiin, 1,3-oxathiane, 1,4-oxathiin, 1,4-oxathiane, 2H-1,2-thiazine, tetrahydro-1,2-thiazine, 2H-1, 3-thiazine,

4H-1, 3-thiazine, 5, 6-dihydro-4H-thiazine, 4H-1, 4-thiazine, tetrahydro-1, 4-thiazine, 2H-1, 2-oxazine, 4H-1, 2-oxazine, 6H-1, 2-oxazine, 2H-1,3-oxazine, 4H-1,3-oxazine, 4H-1, 4-oxazine, morpholine, trioxane, 4H-1, 2,3-trithiin, 1,2, 3-trithiane, 1,3, 5-trithiane, hexahydro-1,3, 5-triazine, tetrahydrothiophene, tetrahydrofuran, pyrroline, pyrrolidine, pyrrolidone, pyrrolidione, pyrazoline, pyrazolidine, imidazoline, imidazolidine, 1,2-dioxole, 1,2-dioxolane, 1,3-dioxole, 1, 3-dioxolane, 3H-1,2-dithiole, 1, 2-dithiolane, 1,3-dithiole, 1,3-dithiolane, isoxazoline, isoxazolidine, oxazoline, oxazolidine, thiazoline, thiozolidine, 3H-1, 2-oxathiole, 1,2-oxathiolane, 5H-1,2-oxathiole, 1,3-oxathiole, 1,3-oxathiolane, 1,2, 3-trithiole, 1,2, 3-trithiolane, 1,2, 4-trithiolane, 1,2, 3- trioxole, 1,2, 3-trioxolane. 1,2, 4-trioxolane, 1,2, 3-triazoline and 1,2, 3-triazolidine.

[0042] 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.

[0043] Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I respectively.

[0044] The invention includes various isotopically labeled compounds as defined herein, for example, those into which radioactive isotopes such as ^{3}H, ^{13}C, and ^{14}C , are present. Such isotopically labelled compounds are useful in metabolic studies (with, for example, ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In other examples, an ^{18}F or labeled compound may be used for PET or SPECT studies. Isotopic variations of the compounds have the potential to change a compound's metabolic fate and/or create small changes in physical properties such as hydrophobicity, and the like.

Isotopic variations also have the potential to enhance efficacy and safety, enhance bioavailability and half-life, alter protein binding, change biodistribution, increase the proportion of active metabolites and/or decrease the formation of reactive or toxic metabolites. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[0045] 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

[0046] 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.

[0047] In one aspect, the compounds of the invention may 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.

[0048] In another aspect, the compounds of the invention 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).

[0049] 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.

[0050] The compounds of the invention 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 pClneo™ (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)).

[0051] 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^{TM} 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 and 20 mM EDTA is added to each well. Cell lysis is completed within 60 min at room temperature and total amount of YOPRO^{TM} 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.

[0052] 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), inflammatory eye diseases, e.g. Sjoegren's syndrome, keratoconjunctivitis or uveitis, inflammatory bowel disease, Crohn's disease or ulcerative colitis.

[0053] 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 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 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 any one of the examples, or a pharmaceutically acceptable salt thereof;

(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

[0054] 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.

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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).

[0059] 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.

[0060] 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.

[0061] 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.

[0062] 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.

[0063] 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.

[0064] 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.

[0065] 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.

[0066] 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.

[0067] 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.

[0068] 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 hercin, 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

[0069] General procedures for preparing compounds of the invention are described in the Examples, *infra*. In the reactions described, reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, may be protected to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice (see e.g., T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991).

[0070] 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. A compound of the invention in a base addition salt form may be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.). 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 is to be understood as referring also to the corresponding salts, as appropriate.

[0071] 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), (3) and (4), 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), (3) and (4), with a basic nitrogen atom.

[0072] 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. 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).

[0073] 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.

[0074] 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).

[0075] 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.

[0076] 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.

[0077] In summary, the compounds of the invention may be made by a process as described in the Examples; and

(a) optionally converting a compound of the invention into a pharmaceutically acceptable salt;

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

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

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

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

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

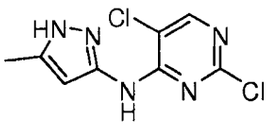
(g) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

[0078] 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.

Intermediate 1

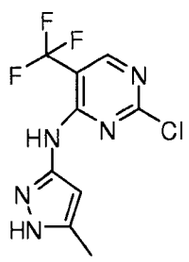
2,5-dichloro-N-(5-methyl-1H-pyrazol-3-yl)pyrimidin-4-amine



[0079] A mixture of 5-methyl-1H-pyrazol-3-amine (3.00 g, 30.9 mmol), 2,4,5-trichloropyrimidine (5.67 g, 30.9 mmol, 1 equiv.) and Na_2CO_3 (3.60 g, 34.0 mmol, 1.1 equiv.) in EtOH (100 mL) was heated at 40 °C for 24 h. The solvent was removed *in vacuo*. The resulting residue was partitioned between EtOAc (350 mL) and water (100 mL). The EtOAc layer was washed with water (3x), saturated aqueous NaCl (1x) and dried over Na_2SO_4. The resulting EtOAc solution was concentrated *in vacuo*, providing the product 2,5-dichloro-N-(5-methyl-1H-pyrazol-3-yl)pyrimidin-4-amine; ESMS *m/z* 244.0 ($M + H^+$).

Intermediate 2

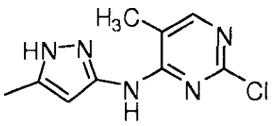
2-chloro-N-(5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-4-amine



[0080] A mixture of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (1.06 g, 4.86 mmol), 5-methyl-1H-pyrazol-3-amine (472.2 mg, 4.86 mmol) and sodium carbonate (2.06 g, 19.4 mmol) in 100 mL of EtOH was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo*. The crude solid was partitioned between EtOAc and water. The combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo*, and purified by silica chromatography (EtOAc/ hexanes: 1/1) to afford 2-chloro-N-(5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-4-amine; ESMS *m/z* 278.0 ($M + H^+$).

Intermediate 3

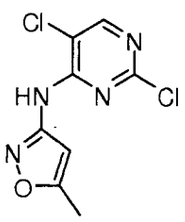
2-chloro-5-methyl-N-(5-methyl-1H-pyrazol-3-yl)pyrimidin-4-amine



[0081] A mixture of 5-methyl-1H-pyrazol-3-amine (3.00 g, 30.9 mmol), 2,4-dichloro-5-methylpyrimidine (5.03 g, 30.9 mmol, 1 equiv.) and Na_2CO_3 (3.60 g, 34.0 mmol, 1.1 equiv.) in EtOH (100 mL) was heated at 40 °C for 24 h. The solvent was removed *in vacuo*. The resulting residue was partitioned between EtOAc (350 mL) and water (100 mL). The EtOAc layer was washed with water (3x), saturated aqueous NaCl (1x), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting crude product was sonicated in Et_2O (200 mL) and the resulting precipitate collected by filtration. This powder was further washed with Et_2O, providing the product 2-chloro-5-methyl-N-(5-methyl-1H-pyrazol-3-yl)pyrimidin-4-amine; ESMS *m/z* 224.1 ($M + H^+$).

Intermediate 4

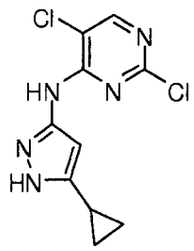
N-(2,5-dichloropyrimidin-4-yl)-5-methylisoxazol-3-amine



[0082] The mixture 5-methylisoxazol-3-amine (98 mg, 1.0 mmol), 2,4,5-trichloropyrimidine (344 μL, 3.0 mmol), and sodium carbonate (106 mg, 1.0 mmol) in 3 mL of EtOH was heated at 60°C overnight. The reaction mixture was concentrated and then partitioned between EtOAc and brine. The collected organic extracts were dried (Na_2SO_4), concentrated *in vacuo*, and purified with silica gel chromatography (MeOH/DCM: 1/9) to afford N-(2,5-dichloropyrimidin-4-yl)-5-methylisoxazol-3-amine; ESMS *m/z* 245.0 ($M + H^+$).

Intermediate 5

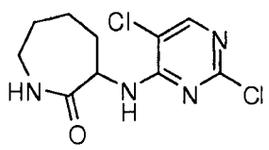
2,5-dichloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)pyrimidin-4-amine



[0083] A mixture of 5-cyclopropyl-1H-pyrazol-3-amine (246 mg, 2.00 mmol), 2,4,5-trichloropyrimidine (367 mg, 2.00 mmol, 1 equiv.) and Na_2CO_3 (233 mg, 2.20 mmol, 1.1 equiv.) in EtOH (10 mL) was heated at 40 °C for 16 h. The crude reaction mixture was diluted with EtOAc and sequentially washed with: water (3x) and saturated aqueous NaCl (1x). The resulting EtOAc layer was dried over Na_2SO_4 and then concentrated *in vacuo*, providing 2,5-dichloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)pyrimidin-4-amine; ESMS *m/z* 270.0 ($M + H^+$).

Intermediate 6

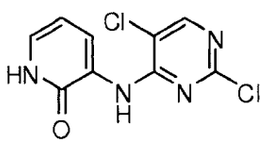
3-(2,5-dichloropyrimidin-4-ylamino)azepan-2-one



[0084] A mixture of (±)-α-amino-ε-caprolactam (256 mg, 2.0 mmol), 2,4,5-trichloropyrimidine (366 mg, 2.0 mmol, 1 equiv.) and $NaHCO_3$ (168 mg, 2 mmol, 1 equiv.) in a mixture of MeOH (12 mL) and H_2O (6 mL) was stirred at room temperature for 15 h. The resulting precipitate was collected by vacuum filtration and washed with small amounts of MeOH and water, providing the product 3-(2,5-dichloropyrimidin-4-ylamino)azepan-2-one; ESMS *m/z* 275.0 ($M + H^+$).

Intermediate 7

3-(2,5-dichloropyrimidin-4-ylamino)pyridin-2(1H)-one

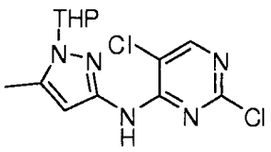


[0085] A mixture of 3-aminopyridin-2(1H)-one (99 mg, 0.90 mmol), 2,4,5-trichloropyrimidine (165 mg, 0.90 mmol, 1 equiv.) and $NaHCO_3$ (76 mg, 0.90 mmol, 1 equiv.) in a mixture of MeOH (6 mL) and H_2O (3 mL) was stirred at room

temperature for 24 h. The resulting precipitate was collected by vacuum filtration and washed with small amounts of MeOH and water, providing the product 3-(2,5-dichloropyrimidin-4-ylamino)pyridin-2(1H)-one; ESMS *m/z* 257.0 ($M + H^+$).

Intermediate 8

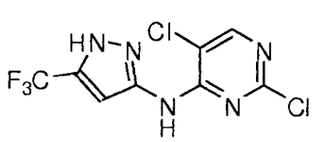
2,5-Dichloro-N-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)pyrimidin-4-amine



[0086] To a mixture of 2,5-dichloro-N-(5-methyl-1H-pyrazol-3-yl)pyrimidin-4-amine (2.44 g, 10 mmol) and 4-toluenesulfonic acid monohydrate (1.9g, 10 mmol) in THF (200 mL), was added DHP (4.25g, 50 mmol). After stirring overnight, the reaction turned clear. After concentration, the residue was dissolved in ethyl acetate and washed with Na_2CO_3 saturated aqueous solution. The organic layer was then washed with brine, dried over sodium sulfate and concentrated *in vacuo* to afford 2,5-Dichloro-N-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)pyrimidin-4-amine as light yellow solid, which was used in subsequent reactions without further purification; ESMS *m/z* 244 ($M-THP+H^+$); TLC Rf=0.6 (Silica; 1:1 ethyl acetate/hexanes; starting material Rf=0.2).

Intermediate 9

2,5-Dichloro-*N*-(5-(trifluoromethyl)-1*H*-pyrazol-3-yl)pyrimidin-4-amine



Step 1: 5-(Trifluoromethyl)-1*H*-pyrazol-3-amine

[0087] A mixture of (*E*)-4-amino-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (5.00 g, 27 mmol) and hydrazine (1.05 g) in anhydrous EtOH (20 mL) was stirred at 80 °C in a sealed vial overnight. The reaction was quenched with water (50 mL), and extracted with EtOAc (100ml, then 2x50 mL). The EtOAc layers were combined and

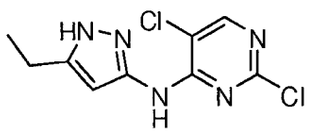
sequentially washed with water (25 mL), brine (25 mL), dried over Na_2SO_4 and evaporated to give a light brown oily residue. The crude product was purified by silica chromatography (30-100% EtOAc in hexanes gradient) to give 5-(trifluoromethyl)-1*H*-pyrazol-3-amine as an off white solid; ESMS m/z 152.0 ($M+H^+$).

Step 2: 2,5-Dichloro-*N*-(5-(trifluoromethyl)-1*H*-pyrazol-3-yl)pyrimidin-4-amine

[0088] A mixture of 5-(trifluoromethyl)-1*H*-pyrazol-3-amine (500 mg, 3.3 mmol), 2,4,5-trichloropyrimidine (607 mg, 3.3 mmol) and sodium carbonate (525 mg, 5 mmol) in anhydrous EtOH (10 mL) was stirred at rt. After one day, LCMS showed the reaction was not complete. Additional 2,4,5-trichloropyrimidine (0.15 mL) and sodium carbonate (525 mg) were added and the reaction continued for two more days. The solvent was evaporated, and the residue was extracted with DCM (3x20 mL). The combined DCM layers were washed with brine (10 mL), dried over Na_2SO_4 and evaporated. The crude product was purified by silica chromatography (0-50% EtOAc in hexanes gradient) to give 2,5-Dichloro-*N*-(5-(trifluoromethyl)-1*H*-pyrazol-3-yl)pyrimidin-4-amine as a light tan colored solid; ESMS m/z 297.9 ($M+H^+$).

Intermediate 10

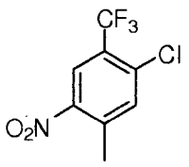
2,5-Dichloro-*N*-(5-ethyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine



[0089] A mixture of 5-ethyl-1*H*-pyrazol-3-amine (1.00 g, 6.77 mmol), 2,4,5-trichloropyrimidine (1.24 g, 6.77 mmol) and Na_2CO_3 (1.79 g, 16.9 mmol) in *iso*-propanol (15 mL) was stirred in a sealed vial at rt for two days. Water (10 mL) was added. The solid was collected by filtration, washed with water (10 mL) and dried to give 2,5-Dichloro-N-(5-ethyl-1H-pyrazol-3-yl)pyrimidin-4-amine as a light yellow solid; ESMS m/z 258.0 ($M+H^+$).

Intermediate 11

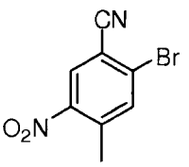
1-chloro-5-methyl-4-nitro-2-(trifluoromethyl)benzene



[0090] To a solution of 2-chloro-4-methyl-1-(trifluoromethyl)benzene (6.65g, 34.1 mmol) in conc. sulfuric acid (25 mL) at 0 °C was added potassium nitrate (3.46 g, 34.1 mmol) in sulfuric acid (15 mL). After stirring at 0 °C for 1.5 h, the reaction mixture was poured into 500 mL of ice water. The precipitate was collected by filtration and washed with copious amounts of water, yielding 1-chloro-5-fluoro-4-nitro-2-(trifluoromethyl)benzene as an orange solid; ^{1}H NMR (400 MHz, chloroform-d) δ 8.356 (s, 1H), 7.543 (s, 1H), 2.660 (s, 3H).

Intermediate 12

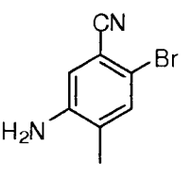
2-Bromo-4-methyl-5-nitrobenzonitrile



[0091] Following the same procedure as described in Intermediate 11 starting with 2-bromo-4-methylbenzonitrile, 2-bromo-4-methyl-5-nitrobenzonitrile was obtained as a yellow solid; ^{1}H NMR (400 MHz, chloroform-d) δ 8.290 (s, 1H), 7.742 (s, 1H), 2.683 (s, 3H).

Intermediate 13

5-Amino-2-bromo-4-methylbenzonitrile

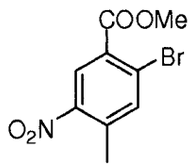


[0092] To a solution of 2-bromo-4-methyl-5-nitrobenzonitrile (500mg, 2.07 mmol) in ethanol (20mL) was added tin chloride (785mg, 4.14 mmol). The mixture was refluxed for 5 h. After cooling to room temperature, triethylamine (1.01g, 10 mmol) was added. The mixture was concentrated and purified by silica

chromatography (30-50% ethyl acetate in hexanes gradient) to afford 5-Amino-2-bromo-4-methylbenzonitrile a as beige solid; ESMS *m/z* 211 ($M + H^+$).

Intermediate 14

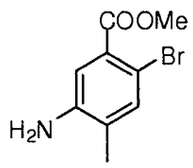
Methyl 2-bromo-4-methyl-5-nitrobenzoate



[0093] Following the same procedure as described in Intermediate 11 starting with methyl 2-bromo-4-methylbenzoate, the title compound was obtained as a white solid; ^1H NMR (400 MHz, chloroform-d) δ 8.505 (s, 1H), 7.711 (s, 1H), 3.967 (s, 3H), 2.640 (s, 3H).

Intermediate 15

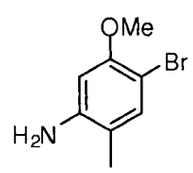
Methyl 5-amino-2-bromo-4-methylbenzoate



[0094] Following the same procedure as described in Intermediate 13, the title compound was obtained as a beige solid; ESMS *m/z* 244 ($M + H^+$).

Intermediate 16

4-Bromo-5-methoxy-2-methylaniline



Step 1: N-(5-methoxy-2-methylphenyl)acetamide

[0095] To a solution of triethylamine (2.9 g, 14.4 mmol) and 5-methoxy-2-methylaniline (1.0 g, 7.2 mmol) in DCM (30 mL) at 0 °C, was added acetyl chloride

(0.57 g, 7.2 mmol) dropwise. The mixture was stirred at room temperature for 1 hour. The reaction was quenched with saturated ammonium chloride aqueous solution, and extracted with DCM. The organic layer was dried over Na_2SO_4 and concentrated to give N-(5-methoxy-2-methylphenyl)acetamide as needle-shaped crystals. The crude product was used in the next step without further purification.

Step 2: N-(4-bromo-5-methoxy-2-methylphenyl)acetamide

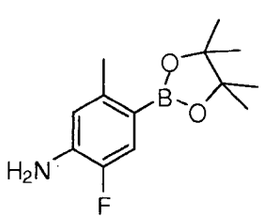
[0096] To a solution of N-(5-methoxy-2-methylphenyl)acetamide in acetic acid (40 mL) was added Br_2 (3 g, 19 mmol) slowly. The mixture was capped and stirred at 50 °C for 5 hours. The reaction was cooled to room temperature, then quenched with sodium sulfite aqueous solution, and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated to give crude N-(4-bromo-5-methoxy-2-methylphenyl)acetamide as a brown oil, which was used in the next step without further purification.

Step 3: 4-bromo-5-methoxy-2-methylaniline

[0097] N-(4-bromo-5-methoxy-2-methylphenyl)acetamide was dissolved in methanol (15 mL) and concentrated HCl (30 mL). The mixture was refluxed at 95 °C overnight. After cooling to room temperature, the mixture was poured into ice water, and basified to pH = 12 with conc. NaOH aqueous solution. The mixture was then extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica chromatography (15% ethyl acetate in hexanes) to give 4-bromo-5-methoxy-2-methylaniline as a beige solid; ^1H NMR (400 mHz, $CDCl_3$) 7.20 (s, 1H), 6.37 (s, 1H), 4.6 (br, 2H), 3.82 (s, 3H), 2.12 (s, 3H).

Intermediate 17

2-Fluoro-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

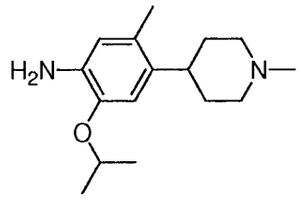


[0098] A mixture of 4-bromo-2-fluoro-5-methylaniline (2.0 g, 9.8 mmol),

bis(pinacolato)diboron (2.74 g, 10.8 mmol), tricyclohexylphosphine (274.8 mg, 0.98 mmol), $Pd_2(dba)_3$ (448.9 mg, 0.49 mmol), and potassium acetate (1.92 g, 19.6 mmol) in 60 mL of 1,4-dioxane was degassed and purged with nitrogen. The reaction mixture was heated at 80°C overnight and then cooled to room temperature. The mixture was partitioned between EtOAc and water and the collected organic extracts were dried (Na_2SO_4), concentrated *in vacuo*, and purified by silica chromatography (EtOAc / Hexanes: 20/ 80) to afford 2-fluoro-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline; ESMS *m/z* 252.2 ($M + H^+$).

Intermediate 18

2-Isopropoxy-5-methyl-4-(1-methyl-piperidin-4-yl)-phenylamine



Step 1: 1-bromo-5-fluoro-2-methyl-4-nitrobenzene

[0099] To a solution of 2-bromo-4-fluoro-1-methylbenzene (5 g, 26.4 mmol) dissolved in conc. sulfuric acid (20 mL) was added potassium nitrate (2.67 g, 26.4 mmol) in sulfuric acid (5 mL) at 0 °C. After stirring at 0 °C for 1hr, the reaction was diluted with water, extracted with ethyl acetate (3 x 40 mL). The combined organic phases were washed with saturated sodium bicarbonate solution and brine sequentially, and then dried over Na_2SO_4. The crude product obtained after concentration was purified by silica gel column chromatography with mixed solvent hexanes/EtOAc (95/5) to afford 1-bromo-5-fluoro-2-methyl-4-nitrobenzene as an orange solid. ^1H NMR (400 MHz, chloroform-d) δ 7.93 (d, 1H, J = 7.6 Hz), 7.50 (d, 1H, J = 10 Hz), 2.43 (s, 3H).

Step 2: 1-bromo-5-isopropoxy-2-methyl-4-nitrobenzene

[0100] To a solution of 1-bromo-5-fluoro-2-methyl-4-nitrobenzene (Step 1, 1.5 g, 6.4 mmol) in 2-propanol (30 mL) was added cesium carbonate (5.3 g, 16 mmol). The mixture was heated at 50 °C overnight. The mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was concentrated and the residue

was purified with silica gel column chromatography with 5% ethyl acetate in hexanes to afford 1-bromo-5-isopropoxy-2-methyl-4-nitrobenzene as a yellow solid.

Step 3: 4-(5-Isopropoxy-2-methyl-4-nitrophenyl)pyridine

[0101] To a mixture of 1-bromo-5-isopropoxy-2-methyl-4-nitrobenzene (Step 2, 1g, 3.65 mmol), pyridine-4-boronic acid (490 mg, 4 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (300 mg, 0.73 mmol) and potassium phosphate (1.55g, 7.3 mmol) in mixed solvent of dioxane (15 mL) and water (7.5 mL) was added tris(dibenzylidene-acetone)dipalladium (0) (334mg, 0.36 mmol). This mixture was sealed and purged with nitrogen for 3 minutes and then heated at 120 °C for 5 hours. The mixture was cooled to room temperature, filtered, and the filtrate was concentrated. After concentration, the crude product was purified with silica gel flash column chromatography (60% ethyl acetate in hexanes) to afford 4-(5-isopropoxy-2-methyl-4-nitrophenyl)pyridine a as yellow solid: ESMS *m/z* 273.2 ($M + H^+$).

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

[0102] 4-(5-Isopropoxy-2-methyl-4-nitro-phenyl)-pyridine (Step 3, 217 mg, 0.797 mmol) was dissolved in anhydrous THF (9 mL). Iodomethane (0.10 mL, 1.61 mmol, 2 equiv.) was added, and the reaction was stirred at 40 °C in a sealed tube for 2 days. The volatiles were 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+).

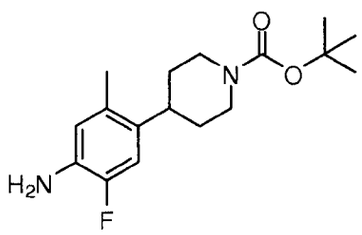
Steps 5 and 6: 2-Isopropoxy-5-methyl-4-(1-methyl-piperidin-4-yl)-phenylamine

[0103] 4-(5-Isopropoxy-2-methyl-4-nitro-phenyl)-1-methyl-pyridinium iodide (Step 4, 0.697 mmol) was dissolved in CH_3OH (20 mL) and cooled to 0 °C. $NaBH_4$ (264 mg, 6.97 mmol, 10 equiv.) was slowly added. After this addition was complete, the cooling bath was removed and the reaction was stirred at room temperature for 1 h. The reaction was quenched by the slow addition of 1N aqueous HCl (14 mL). The CH_3OH was partially removed by vacuum. The resulting residue was partitioned between EtOAc and 1 N aqueous NaOH. Additional 50 % aqueous NaOH was added until the aqueous layer had a pH >12. The EtOAc layer was washed with 1 N aqueous NaOH (2x), the organic layer was then dried over sodium sulfate, filtered,

and concentrated under vacuum. After concentration, the crude product (175 mg) was dissolved in acetic acid (10 mL). TFA (0.15 mL, 3 equiv.) and PtO_2 (53 mg, 30% w/w) were added and the reaction was placed under 50 psi H_2 gas in a Parr Shaker for 14 h. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The resulting residue was partitioned between EtOAc and 1 N aqueous NaOH. Additional 50% aqueous NaOH was added until the aqueous layer has a pH >12. The EtOAc layer was washed with 1 N aqueous NaOH (2x), the organic layer was then dried over sodium sulfate, filtered, and concentrated under vacuum to give 2-isopropoxy-5-methyl-4-(1-methyl-piperidin-4-yl)-phenylamine, which was used in subsequent steps without further purification: ESMS m/z 263.2 (M + H+).

Intermediate 19

tert-butyl 4-(4-amino-5-fluoro-2-methylphenyl)piperidine-1-carboxylate



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

[0104] A solution of *N-tert*-Butoxycarbonyl-4-piperidone (10.17 g, 0.05 mol) in THF (100 mL) was 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 was 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 was warmed to room temperature and stirred for 3 h. The reaction was quenched at 0 °C with 100 mL of saturated aqueous NH_4Cl and filtered through Celite. The filtrate was added to 100 mL of EtOAc, and the layers were separated. The organic layer was washed with H_2O, dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel chromatography (0-30% EtOAc in Hexanes as eluent and checked by TLC stained with 2% of KMnO4 in EtOH) to afford 4-Trifluoromethanesulfonyloxy-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl

ester as a yellow oil.

Step 2: *Tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate

[0105] A solution of tert-butyl 4-(trifluoromethylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (16.0 g, 48.2 mmol) in DMSO (200 mL) was treated with bis(pinacolato)diboron (12.6 g, 49.6 mmol), potassium acetate (14.65 g, 149 mmol) and Pd(dppf)Cl_2 (790 mg, 0.96 mmol). The solution was purged with N_2 (g) for 5 minutes, and then sealed and heated at 80 °C for 15 h. The reaction was cooled to room temperature and poured into ice water. The mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with brine, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified with silica gel chromatography (15% ethyl acetate in hexanes) to afford tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate as a white solid.

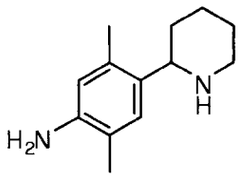
Steps 3 and 4: *Tert*-butyl 4-(4-amino-5-fluoro-2-methylphenyl)piperidine-1-carboxylate

[0106] To a mixture of 5'-chloro-N,2'-dimethyl-4'-nitrobiphenyl-4-carboxamide (204 mg, 1 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (370 mg, 1.2 mmol) and sodium carbonate (742 mg, 7 mmol) in DMF/H_2O (12/3 mL) was added tetrakis(triphenylphosphine) palladium (0) (58 mg, 5% mmol). The reaction tube was sealed, the mixture was purged with N_2 for 3 min and then heated at 90°C under N_2 for overnight. The reaction was cooled to room temperature, and poured into saturated aqueous ammonia chloride solution. The crude reaction mixture was extracted with ethyl acetate (3 x 15 mL). The organic extracts were combined, washed with brine and concentrated. The crude product was purified with silica gel chromatography (20% ethyl acetate in hexanes) to afford *tert*-butyl 4-(4-amino-5-fluoro-2-methylphenyl)-5,6-dihydropyridine-1(2H)-carboxylate as a yellow oil. The obtained oil was dissolved in methanol (20 mL). To the solution was added Pd/C (10%). The reaction mixture was degassed and purged with H_2 for several times and stirred under H_2 (1 atm) overnight. The mixture was filtered and concentrated to afford the *tert*-butyl 4-(4-amino-5-fluoro-2-methylphenyl)piperidine-1-carboxylate as a white solid. ESMS *m/z* 207 (M -Boc+

H^+).

Intermediate 20

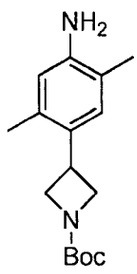
2,5-Dimethyl-4-(piperidin-2-yl)aniline



[0107] To a mixture of 1-bromo-2,5-dimethyl-4-nitrobenzene (185 mg, 1 mmol) and 2-(tributylstannyl)pyridine (202 mg, 1.1 mmol) in DMF (4 mL) was added tetrakis(triphenylphosphine) palladium (0) (58 mg, 5% mmol). The reaction tube was sealed, the mixture was purged with N_2 for 3 min and then heated at 120 °C under N_2 for overnight. The reaction was cooled to room temperature and poured into saturated aqueous ammonia chloride solution. The crude reaction mixture was extracted with ethyl acetate (3 x 15 mL). The organic extracts were combined, washed with brine and concentrated. The crude product was purified with silica gel column chromatography (60% ethyl acetate in hexanes) to afford 2-(2,5-dimethyl-4-nitrophenyl)pyridine as a white solid. The obtained solid was dissolved in acetic acid/TFA (15 mL/200 uL). To this solution was added PtO_2 (10% w/w). The reaction mixture was degassed and purged with H_2 for several times and stirred under 1 atm. hydrogen gas overnight. The mixture was filtered and concentrated to afford 2,5-Dimethyl-4-(piperidin-2-yl)aniline as a yellow oil. ESMS m/z 205 ($M + H^+$).

Intermediate 21

tert-butyl 3-(4-amino-2,5-dimethylphenyl)azetidine-1-carboxylate



Step 1: *tert*-Butyl 3-(2,5-dimethyl-4-nitrophenyl)azetidine-1-carboxylate

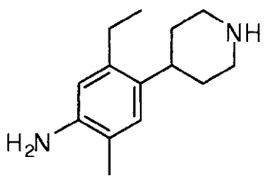
[0108] Prepared from *tert*-butyl 3-iodoazetidine-1-carboxylate and 1-bromo-2,5-dimethyl-4-nitrobenzene by following the general protocol as described in Billotte, S. *Synlett* 1998, 379.

Step 2: tert-butyl 3-(4-amino-2,5-dimethylphenyl)azetidine-1-carboxylate

[0109] *tert*-Butyl 3-(2,5-dimethyl-4-nitrophenyl)azetidine-1-carboxylate was reduced to *tert*-butyl 3-(4-amino-2,5-dimethylphenyl)azetidine-1-carboxylate by standard Raney Ni hydrogenation at room temperature using MeOH as the solvent.

Intermediate 22

5-Ethyl-2-methyl-4-(piperidin-4-yl)aniline



Step 1: *tert*-butyl 4-(4-amino-5-methyl-2-vinylphenyl)-5,6-dihydropyridine-1(2H)-carboxylate

[0110] To a mixture of 4-bromo-5-chloro-2-methylaniline (500 mg, 2.27mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (840 mg, 3.73 mmol) and sodium carbonate (2.52 g, 15.9 mmol) in DMF/H_2O (20/5 mL) was added tetrakis(triphenylphosphine) palladium (0) (131 mg, 5 mol%). The reaction tube was sealed, the mixture was purged with N_2 for 3 min and then heated at 100°C under N_2 for overnight. The reaction was cooled to room temperature and poured into saturated aqueous ammonia chloride solution. The crude reaction mixture was extracted with ethyl acetate (3 x 15 mL). The organic extracts were combined, washed with brine and concentrated. The crude product was purified with silica chromatography (80% ethyl acetate in hexanes) to afford *tert*-butyl 4-(4-amino-2-chloro-5-methylphenyl)-5,6-dihydropyridine-1(2H)-carboxylate as a yellow solid. This obtained product (322 mg, 1 mmol) was dissolved in dioxane/NMP (anhydrous, 4 mL, 3/1). To this solution was added tributyl(vinyl)stannane (380 mg, 1.2 mmol), cesium fluoride (304 mg, 2 mmol) and palladium bis(tri-tert-butyl-

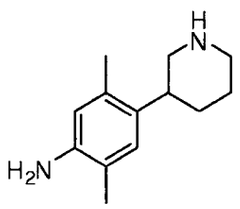
phosphine) (51 mg, 10 mol%). This mixture was purged with N_2 for 3 minutes and then heated in a sealed tube at 120 °C for overnight. The mixture was cooled to room temperature and diluted with ethyl acetate. The resulting mixture was sequentially washed with saturated aqueous ammonium chloride and brine, and finally dried over sodium sulfate. After concentration, the crude product was purified via silica chromatography (10% ethyl acetate in hexanes) to afford *tert*-butyl 4-(4-amino-5-methyl-2-vinylphenyl)-5,6-dihydropyridine-1(2H)-carboxylate as a light yellow oil; ESMS *m/z* 215.2 (M -Boc + H^+).

Step 2: 5-Ethyl-2-methyl-4-(piperidin-4-yl)aniline

[0111] The product obtained from the previous step was dissolved in methanol (20 mL). To this solution was added conc. aqueous HCl (200 uL) and platinum oxide (23 mg, 0.1 mmol). The reaction mixture was degassed and purged with H_2 for several times and vigorously stirred under 1 atm. H_2 for 3 h. The mixture was filtered and concentrated to afford 5-Ethyl-2-methyl-4-(piperidin-4-yl)aniline as a yellow solid. ESMS *m/z* 219.2 (M + H^+).

Intermediate 23

2,5-Dimethyl-4-(piperidin-3-yl)aniline



Step 1: 2,5-Dimethyl-4-(pyridin-3-yl)aniline

[0112] A suspension of 4-bromo-2,5-dimethylaniline (4.00 g, 20 mmol), pyridin-3-ylboronic acid (2.70 g, 11 mmol), $Pd_2(dba)_3$ (0.55 g, 0.6 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.98 g, 1.2 mmol) and Na_2CO_3 (10.6 g, 100 mmol) in n-BuOH (50 mL) was degassed by a stream of argon gas for 15 min. The reaction flask was sealed and placed in a pre-heated oil bath (115 °C). After stirring overnight, the reaction was cooled and filtered. The filter cake was washed with DCM and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in EtOAc (150 mL). EtOAC was sequentially washed with water (20 mL),

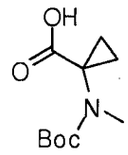
brine (20 mL), dried over Na_2SO_4 and evaporated. The crude product was purified by silica chromatography (0-50% EtOAC in hexanes gradient) to give 2,5-dimethyl-4-(pyridin-3-yl)aniline as a yellow solid; ESMS m/z 199.1 ($M+H^+$).

Step 2: 2,5-Dimethyl-4-(piperidin-3-yl)aniline

[0113] 2,5-Dimethyl-4-(pyridin-3-yl)aniline (403 mg, 2.03 mmol) was dissolved in MeOH (5 mL) and conc. aqueous HCl (1 mL), followed by addition of PtO_2 (40 mg). The flask was purged with H_2 and the reaction was vigorously stirred at rt under H_2 (1 atm). After two days, LCMS shows the completion of the reaction. The catalyst was removed by filtration and the remaining solution was concentrated *in vacuo* to give 2,5-Dimethyl-4-(piperidin-3-yl)aniline as a white solid, which can be used in subsequent reactions without further purification; ESMS m/z 205.2 ($M+H^+$).

Intermediate 24

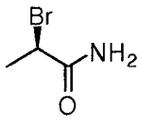
1-(tert-butoxycarbonyl(methyl)amino)cyclopropanecarboxylic acid



[0114] To a solution of 1-(tert-butoxycarbonylamino)cyclopropanecarboxylic acid (201mg, 1.0 mmol) in DMF (2 mL) was added NaH (120 mg, 3.0 mmol) at 0 °C. The resulting mixture was stirred at 0°C for 10 min. before the addition of MeI (568 mg, 4.0 mmol). The mixture was then warmed up to room temperature and stirred for 2 hr. Saturated NH_4Cl aqueous solution (20 mL) was added into the mixture, and the solution was extracted with EtOAc (3 x 10 mL). The combined organic layers were concentrated and the residue was dissolved in MeOH (3 ml) with NaOH (3 N, 1mL). This mixture was stirred at 80 °C for 1 hr and cooled down to room temperature. The clear solution was purified directly on preparative RP-HPLC to provide 1-(tert-butoxycarbonyl(methyl)amino)cyclopropanecarboxylic acid. ESMS *m/z* 238.2 ($M + Na^+$).

Intermediate 25

(*R*)-2-bromopropanamide



Step 1: (*R*)-2-bromopropanoyl chloride

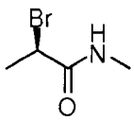
[0115] Under nitrogen, to the solution of (*R*)-2-bromopropanoic acid (5.0 g, 32.68 mmol) in 100 mL of DCM was added thionyl chloride (7.1 mL, 98.04 mmol) and 1 mL of DMF sequentially at 0°C. The reaction was stirred at room temperature overnight, and concentrated *in vacuo*. The resulting crude product was directly used in next step without further purification.

Step 2: (*R*)-2-bromopropanamide

[0116] (*R*)-2-bromopropanoyl chloride was slowly added to a 37% ammonia hydroxide water solution cooled to 0°C. The reaction was allowed to warm to room temperature and was stirred for 2 h. The product was extracted with EtOAc and the collected organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford (*R*)-2-bromopropanamide.

Intermediate 26

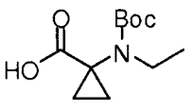
(*R*)-2-bromo-*N*-methylpropanamide



[0117] (*R*)-2-bromopropanoyl chloride was slowly added to a methylamine water solution cooled to 0°C. The reaction was allowed to warm to room temperature and was stirred for 2 h. The product was extracted with EtOAc and the collected organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford (*R*)-2-bromo-*N*-methylpropanamide.

Intermediate 27

1-(*tert*-butoxycarbonyl(ethyl)amino)cyclopropanecarboxylic acid



Step 1: Ethyl 1-(*tert* butoxycarbonyl(ethyl)amino)cyclopropanecarboxylate

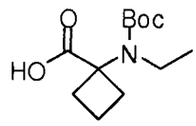
[0118] Under nitrogen, to the solution of 1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylic acid (201.2 mg, 1.0 mmol) in 4 mL of DMF was added NaH (120.0 mg, 3.0 mmol) at 0°C. After 30 min stirring, iodoethane (0.4 mL, 5.0 mmol) was added to the reaction. The reaction was warmed gradually to room temperature and stirred overnight. The reaction mixture was partitioned between EtOAc and water. The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo* to afford crude ethyl 1-(*tert* butoxycarbonyl(ethyl)amino) cyclopropanecarboxylate, which was used in the next step without further purification.

Step 2: 1-(*tert*-butoxycarbonyl(ethyl)amino)cyclopropanecarboxylic acid

[0119] The crude product from Step 1 was dissolved in a mixture of EtOH (4.0 mL) and water (1.0 mL). LiOH (82.0 mg, 2.0 mmol) was added to the reaction. The reaction was heated at 120°C in a microwave reactor for 10 min. The reaction was concentrated *in vacuo*, and the crude product was partitioned between EtOAc and water. The water layer was neutralized with 4N aq. HCl to pH 4 and then extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo* to afford 1-(*tert* butoxycarbonyl(ethyl)amino)cyclopropanecarboxylic acid.

Intermediate 28

1-(*tert*-butoxycarbonyl(ethyl)amino)cyclobutanecarboxylic acid



Step 1: Ethyl 1-(*tert*-butoxycarbonyl(ethyl)amino)cyclobutanecarboxylate

[0120] Under nitrogen, to the solution of 1-(*tert*-butoxycarbonylamino)cyclobutanecarboxylic acid (430.0 mg, 2.0 mmol) in 4 mL of DMF was added NaH (240.0 mg, 6.0 mmol) at 0°C. After stirring for 30 min., iodoethane (0.8 mL, 10.0 mmol) was added to the reaction. The reaction was warmed to room temperature gradually and stirred overnight. The reaction mixture was partitioned between EtOAc and water. The combined organic extracts were dried

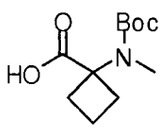
(Na_2SO_4), and concentrated *in vacuo* to afford crude ethyl 1-(*tert*-butoxycarbonyl(ethyl)amino) cyclobutanecarboxylate.

Step 2: 1-(*tert*-butoxycarbonyl(ethyl)amino)cyclobutanecarboxylic acid

[0121] The crude product from Step 1 was dissolved in EtOH (4.0 mL) and water (1.0 mL). LiOH (164.0 mg, 4.0 mmol) was added to the reaction. The reaction was heated at 120°C in a microwave reactor for 10 min. The reaction was concentrated *in vacuo*, and the crude was partitioned between EtOAc and water. The water layer was neutralized with 4N aq. HCl to pH 4 and then extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo* to afford 1-(*tert*-butoxycarbonyl(ethyl)amino) cyclobutanecarboxylic acid.

Intermediate 29

1-(*tert*-butoxycarbonyl(methyl)amino)cyclobutanecarboxylic acid



Step 1: Methyl 1-(*tert*-butoxycarbonyl(ethyl)amino)cyclobutanecarboxylate

[0122] Under nitrogen, to the solution of 1-(*tert*-butoxycarbonylamino) cyclobutanecarboxylic acid (430.0 mg, 2.0 mmol) in 4 mL of DMF was added NaH (240.0 mg, 6.0 mmol) at 0°C. After stirring for 30 min., iodomethane (0.62 mL, 10.0 mmol) was added to the reaction. The reaction was warmed to room temperature gradually and stirred overnight. The reaction mixture was partitioned between EtOAc and water. The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo* to afford crude methyl 1-(*tert*-butoxycarbonyl(ethyl)amino) cyclobutanecarboxylate.

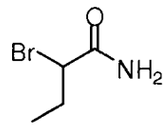
Step 2: 1-(*tert*-butoxycarbonyl(methyl)amino)cyclobutanecarboxylic acid

[0123] The crude product from Step 1 was dissolved in MeOH (4.0 mL) and water (1.0 mL). LiOH (164.0 mg, 4.0 mmol) was added to the reaction. The reaction was heated at 120°C in a microwave reactor for 10 min. The reaction was concentrated *in vacuo*, and the crude was partitioned between EtOAc and water. The water layer was neutralized with 4N aq. HCl to pH 4, and then extracted with EtOAc.

The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo* to afford 1-(*tert*-butoxycarbonyl(methyl)amino) cyclobutanecarboxylic acid.

Intermediate 30

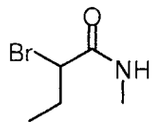
2-bromobutanamide



[0124] Under nitrogen, to a solution of 2-bromobutanoic acid (2.0 g, 12.0 mmol) in DCM (50 mL) at 0°C were sequentially added thionyl chloride (2.6 mL, 35.9 mmol) and 0.5 mL of DMF. The reaction was allowed to warm to room temperature and was stirred overnight. The reaction mixture was concentrated *in vacuo* and then cooled to 0°C. Thirty (30) mL of 37% aqueous ammonia hydroxide was added slowly. The reaction was allowed to warm to room temperature and was stirred for 2 h followed by extraction with EtOAc. The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo* to afford 2-bromobutanamide.

Intermediate 31

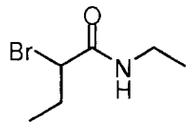
2-bromo-*N*-methylbutanamide



[0125] Under nitrogen, to a solution of 2-bromobutanoic acid (2.0 g, 12.0 mmol) in DCM (50 mL) at 0°C were sequentially added thionyl chloride (2.6 mL, 35.9 mmol) and 0.5 mL of DMF. The reaction was allowed to warm to room temperature and was stirred overnight. The reaction mixture was concentrated *in vacuo* and then cooled to 0°C. Thirty (30) mL of 40% methylamine water solution was added slowly. The reaction was allowed to warm to room temperature and was stirred for 2 h followed by extraction with EtOAc. The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo* to afford 2-bromo-*N*-methylbutanamide.

Intermediate 32

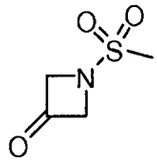
2-bromo-*N*-ethylbutanamide



[0126] Under nitrogen, to a solution of 2-bromobutanoic acid (2.0 g, 12.0 mmol) in DCM (50 mL) at 0°C were sequentially added thionyl chloride (2.6 mL, 35.9 mmol) and 0.5 mL of DMF. The reaction was allowed to warm to room temperature and was stirred overnight. The reaction mixture was concentrated *in vacuo* and then cooled to 0°C. Thirty (30) mL of 40% ethylamine water solution was added slowly. The reaction was allowed to warm to room temperature and was stirred for 2 h, followed by extraction with EtOAc. The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo* to afford 2-bromo-*N*-ethylbutanamide.

Intermediate 33

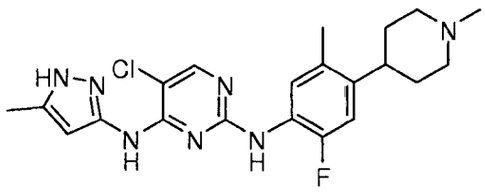
1-(Methylsulfonyl)azetidin-3-one



[0127] To a mixture of 3-azetidinone hydrochloride (471 mg, 3.28 mmol) and K_2CO_3 (1.50 g, 11 mmol) in $CHCl_3/H_2O$ (5/5 mL) was added methanesulfonic anhydride (1.14 g, 6.57 mmol) in one portion at 0 °C. After stirring for 2 h, the reaction was diluted with saturated aqueous $NaHCO_3$ (5 mL) and extracted with DCM (3x25 mL). The combined DCM layers were washed with brine (5 mL), dried over Na_2SO_4 and evaporated to afford 1-(Methylsulfonyl)azetidin-3-one as an off white solid, which was used without further purification; ^1H NMR (400 MHz, $CDCl_3$) δ 4.82 (s, 4H), 3.05 (s, 3H).

Example 1

5-Chloro-N2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (1)

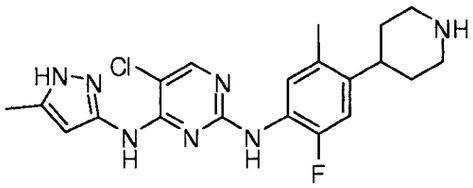


[0128] Step 1: A mixture of 2,5-dichloro-N-(5-methyl-1H-pyrazol-3-yl)pyrimidin-4-amine (Intermediate 1, 132 mg, 0.54 mmol) and *tert*-butyl 4-(4-amino-5-fluoro-2-methylphenyl)piperidine-1-carboxylate (Intermediate 19, 166 mg, 0.54 mmol) in 2-propanol (15 mL) was treated with conc. aqueous HCl (14 drops). The mixture was sealed and heated in a microwave at 130 °C for 60 min. The mixture was concentrated to afford 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as a yellow solid. A portion of the crude product was purified with preparative RP-HPLC to afford 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as a white solid; ESMS *m/z* 416.1 ($M + H^+$). The remainder of the crude product was used directly for the next step without further purification.

[0129] Step 2: To a solution of the crude product from previous step in THF (5 mL) and methanol (5 mL) was added formaldehyde (100 uL, 1.3 mmol) and 10 drops of AcOH sequentially. The reaction mixture was stirred at room temperature for 1 h, then sodium cyanoborohydride (175 mg, 2.78 mmol) was added in one portion, and the reaction was stirred for an additional 30 min. The reaction was quenched by saturated aqueous NH_4Cl and concentrated *in vacuo* to give an oily residue. The residue was purified with preparative RP-HPLC to afford 5-Chloro-N2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as a white solid. ^1H NMR (400 MHz, DMSO-d6) δ 10.33 (br, 1H), 9.90 (br, 1H0, 9.60 (br, 1H), 8.22 (s, 1H), 7.56 (d, 1H), 7.00 (d, 1H), 6.20 (s, 1H), 3.53-3.50 (m, 2H), 3.16-3.10 (m, 2H), 2.97-2.92 (m,1H), 2.81 (d, 3H), 2.26 (s, 3H), 2.16 (s, 3H), 1.94-1.91 (m, 2H), 1.83-1.73 (m, 2H); ESMS *m/z* 430.1 ($M + H^+$).

Example 2

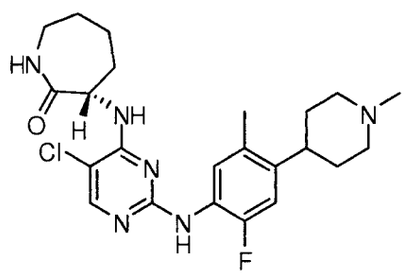
5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (2)



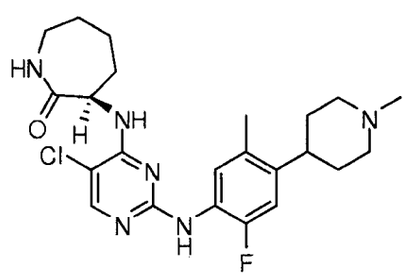
[0130] A mixture of 2,5-dichloro-N-(5-methyl-1H-pyrazol-3-yl)pyrimidin-4-amine (Intermediate 1, 132 mg, 0.54 mmol) and *tert*-butyl 4-(4-amino-5-fluoro-2-methylphenyl)piperidine-1-carboxylate (Intermediate 19, 166 mg, 0.54 mmol) in 2-propanol (15 mL) was treated with conc. aqueous HCl (14 drops). The mixture was sealed and heated in a microwave at 130 °C for 60 min. The mixture was concentrated to afford 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as yellow solid. A portion of the crude product was purified with preparative RP-HPLC to afford 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as a white solid; ESMS *m/z* 416.1 ($M + H^+$).

Examples 3 and 4

(*S*)-3-(5-chloro-2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino) pyrimidin-4-ylamino)azepan-2-one (10)



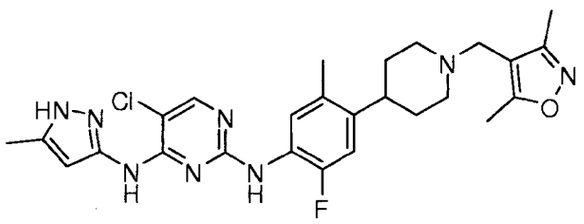
(*R*)-3-(5-chloro-2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino) pyrimidin-4-ylamino)azepan-2-one (11)



[0131] (±)-3-(5-chloro-2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)azepan-2-one was synthesized by the same series of procedures as described in Example 1, utilizing Intermediate 6 and Intermediate 19. Chiral separation of the racemic mixture was conducted with normal phase HPLC using ChiralPaK AD column using the following solvent system: hexanes (80%) and iPrOH (20%) modified with 0.1% Diethylamine. The two purified enantiomer peaks were collected separately: (*S*)-3-(5-chloro-2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)azepan-2-one and (*R*)-3-(5-chloro-2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)azepan-2-one; both peaks: ESMS m/z 461.2 ($M + H^+$). The earlier eluting peak (RT = 7.26 min.) and the later eluting peak (RT = 10.17 min.) were arbitrarily assigned as the (*S*) and (*R*) enantiomer, respectively.

Example 5

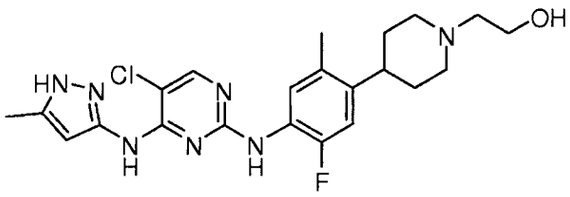
5-Chloro-N2-(4-(1-((3,5-dimethylisoxazol-4-yl)methyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (19)



[0132] To a mixture of 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (0.12 mmol) and triethylamine (83 uL, 0.6 mmol) in DMF (1.5 mL), was added 4-(chloromethyl)-3,5-dimethylisoxazole (35 mg, 0.24 mmol). The mixture was stirred at room temperature for 3 hours. The reaction was filtered and the filtrate was purified by preparative RP-HPLC to afford 5-Chloro-N2-(4-(1-((3,5-dimethylisoxazol-4-yl)methyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as a white solid. 1H NMR (400 MHz, MeOD-d4) 8.12 (s, 1H), 7.75 (d, 1H), 7.03 (s, 1H), 6.27 (s, 1H), 4.25 (s, 2H), 3.69-3.67 (m, 2H), 3.27-3.20 (m, 3H), 2.54 (s, 3H), 2.37 (s, 3H), 2.34 (s, 3H), 2.30 (s, 3H), 2.10-1.95 (m, 4H);ESMS m/z 525.1 (M + H+).

Example 6

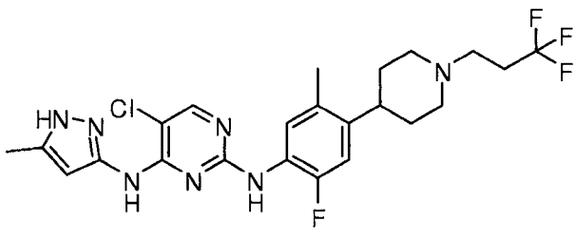
2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)ethanol (22)



[0133] 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (0.12 mmol) was dissolved in anhydrous DMF (1 mL). TEA (50 uL, 0.36 mmol, 3 equiv.) was added followed by 2-bromo-ethanol (0.018 mL, 0.24 mmol, 2 equiv.) dissolved in anhydrous DMF (0.7 mL). The reaction vessel was sealed and heated in a microwave at 100 °C for 20 min. After cooling to room temperature, the reaction was concentrated and the crude product was purified using preparative RP-HPLC to give 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)ethanol as a white solid: ESMS m/z 460.2 (M + H+).

Example 7

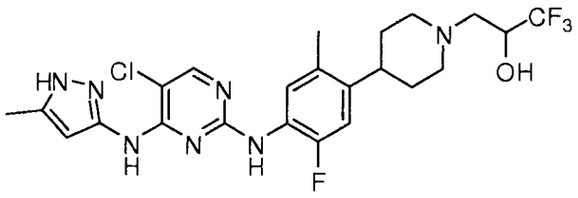
5-chloro-N^2-(2-fluoro-5-methyl-4-(1-(3,3,3-trifluoropropyl)piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (24)



[0134] The mixture of 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (0.12 mmol), 3-bromo-1,1,1-trifluoropropane (85.0 uL, 0.60 mmol) and triethylamine (102.0 uL, 0.60 mmol) in 2 mL of DMF was stirred overnight. The reaction mixture was purified by preparative RP-HPLC to afford 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(3,3,3-trifluoropropyl)piperidin-4-yl)phenyl)- N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine. ESMS m/z 512.2 ($M + H^+$).

Example 8

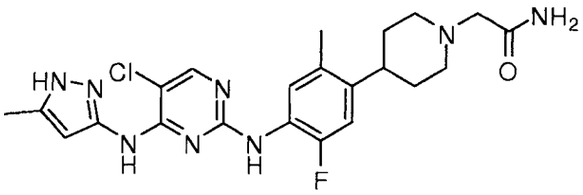
3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol (30)



[0135] The mixture of 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (50.0 mg, 0.12 mmol) and 2-(trifluoromethyl)oxirane (67.8 mg, 0.60 mmol) in 2 mL of DMF was stirred overnight. The reaction mixture was purified by preparative RP-HPLC to afford 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol. ESMS m/z 528.2 ($M + H^+$).

Example 9

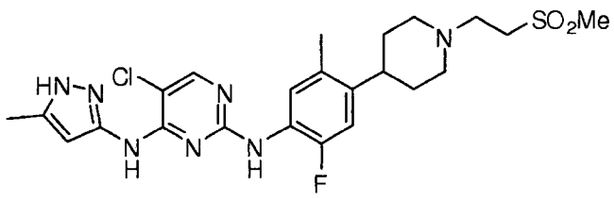
2-(4-(4-(5-Chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)acetamide (39)



[0136] To a mixture of 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (0.12 mmol) and triethylamine (50 uL, 0.36 mmol) in DMF (1.5 mL), was added 2-bromo-acetamide (33 mg, 0.24 mmol). The mixture was stirred at room temperature for 2 hours. The reaction was filtered and the filtrate was purified by preparative RP-HPLC to give 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl) piperidin-1-yl)acetamide as a white solid: ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.11 (s, 1H), 7.76 (d 1H), 7.09 (d, 1H), 6.27 (s, 1H), 4.0 (s, 2H), 3.75-3.73 (m, 2H), 3.22-3.13 (m, 3H), 2.34 (s, 3H), 2.30 (s, 3H), 2.04 -2.00 (m, 4H); ESMS *m/z* 473.2 ($M + H^+$).

Example 10

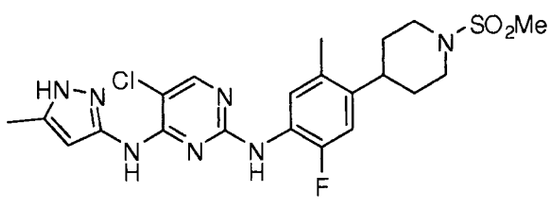
5-Chloro-N2-(2-fluoro-5-methyl-4-(1-(2-(methylsulfonyl)ethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (55)



[0137] To a mixture of 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (0.12 mmol) and triethylamine (83 uL, 0.6 mmol) in DMF (1.5 mL), was added methyl vinyl sulfone (38 mg, 0.36 mmol). The mixture was stirred at room temperature for 1 hour. The reaction was filtered and the filtrate was purified by preparative RP-HPLC to afford 5-Chloro-N2-(2-fluoro-5-methyl-4-(1-(2-(methylsulfonyl)ethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as a white solid. ESMS m/z 522.1 (M + H+).

Example 11

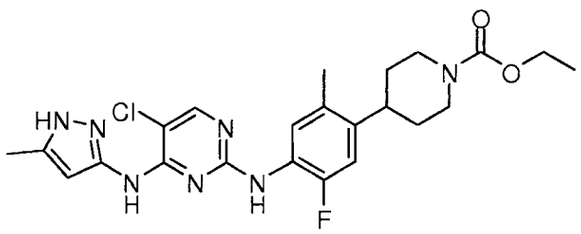
5-Chloro-N2-(2-fluoro-5-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (62)



[0138] To a mixture of 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (0.12 mmol) and triethylamine (50 uL, 0.36 mmol) in DMF (1.5 mL) was added methanesulfonyl chloride (18 uL, 0.24 mmol). The mixture was stirred at room temperature for 2 hours. The reaction was filtered and the filtrate was purified by preparative RP-HPLC to give 5-Chloro-N2-(2-fluoro-5-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as a white solid: ESMS *m/z* 494.2 ($M + H^+$).

Example 12

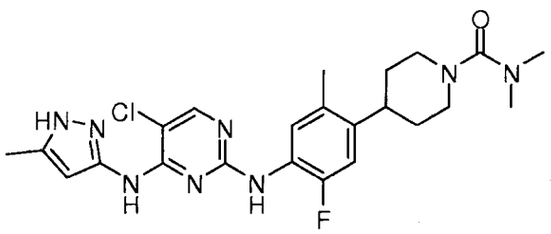
Ethyl 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidine-1-carboxylate (66)



[0139] To a mixture of 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (0.12 mmol) and triethylamine (50 uL, 0.36 mmol) in DMF (1.5 mL) was added ethyl chloroformate (26 mg, 0.24 mmol). The mixture was stirred at room temperature for 2 hours. The reaction was filtered and the filtrate was purified by preparative RP-HPLC to give Ethyl 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidine-1-carboxylate as a white solid: ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.13 (s, 1H), 7.54 (d, 1H), 7.10 (d, 1H), 6.28 (s, 1H), 4.30-4.26 (m, 2H), 4.14 (q, 2H), 2.99-2.96 (m, 3H), 2.33 (s, 3H), 2.29 (s, 3H), 1.8-1.77 (m, 2H), 1.64-1.55 (m, 2H), 1.28 (t, 3H); ESMS *m/z* 488.2 (M + H$^+$).

Example 13

4-(4-(5-Chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)-N,N-dimethylpiperidine-1-carboxamide (69)

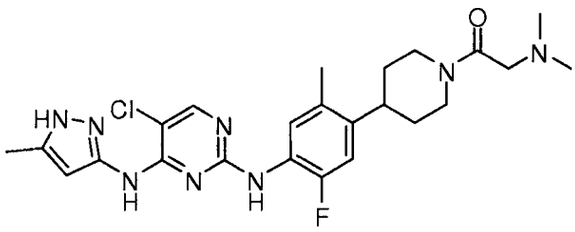


[0140] To a mixture of 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (0.12 mmol) and triethylamine (83 uL, 0.6 mmol) in DMF (1.5 mL) was added dimethylcarbamic chloride (39 mg, 0.36 mmol). The mixture was stirred at room temperature for 1 hour. The reaction was filtered and the filtrate was purified by preparative RP-HPLC to afford 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)-N,N-dimethylpiperidine-1-carboxamide as a white solid.

ESMS m/z 487.2 (M + H+).

Example 14

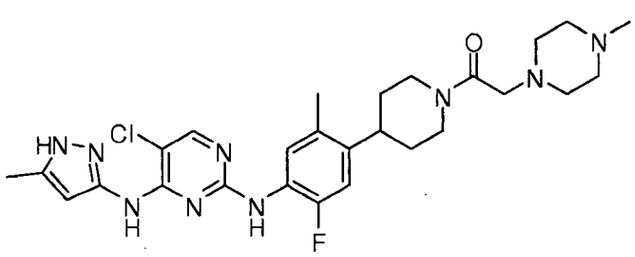
1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone (73)



[0141] To a mixture of 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (0.12 mmol) and triethylamine (50 uL, 0.36 mmol) in DMF (1.5 mL) was added 2-(dimethylamino)acetyl chloride (38 mg, 0.24 mmol). The mixture was stirred at room temperature for 1 hour. The reaction was filtered and the filtrate was purified by preparative RP-HPLC to give 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone as a white solid: ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.08 (s, 1H), 7.71 (d, 1H), 7.03 (d, 1H), 6.26 (s, 1H), 4.71-4.67 (m, 2H), 3.81-3.77 (m, 2H), 3.14-3.12 (m, 2H), 2.98 (s, 3H), 2.96 (s, 3H), 2.90-2.83 (m, 1H), 2.34 (s, 3H), 2.28 (s, 3H), 1.87 (d, 2H), 1.76-1.55 (m, 2H); ESMS *m/z* 501.2 (M + H$^+$).

Example 15

1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(4-methylpiperazin-1-yl)ethanone (105)

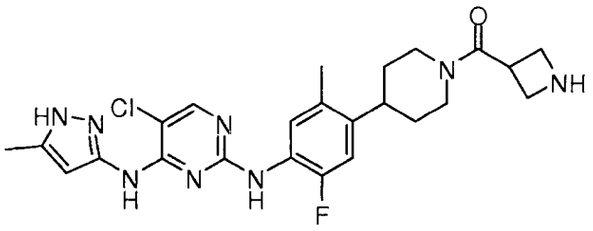


[0142] To the solution of 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (100.0 mg, 0.24 mmol) in 4 mL of DCM was added 2-chloroacetylchloride (23.0 uL, 0.29 mmol) and triethylamine (67.0 uL, 0.48 mmol) sequentially. The reaction was stirred at room

temperature for 1 h then washed by brine. The organic extract was dried over Na_2SO_4, followed by concentration in vacuo to afford a crude product. The crude product was mixed with 1-methylpiperazine (116.0 mg, 1.16 mmol) in 3 mL of DMF and the reaction was stirred overnight at room temperature. The reaction mixture was purified by preparative HPLC to afford 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(4-methylpiperazin-1-yl)ethanone. ESMS m/z 556.3 ($M + H^+$).

Example 16

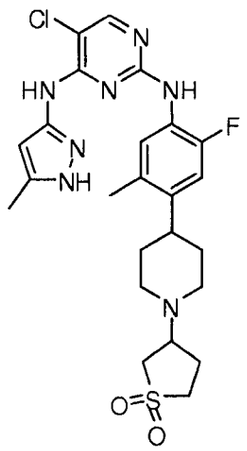
Azetidin-3-yl(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)methanone (131)



[0143] To a mixture of 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (0.12 mmol), di-isopropylethylamine (50 uL, 0.36 mmol) and HATU (55 mg, 0.14 mmol) in DMF (1.5 mL) was added 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid (29 mg, 0.14 mmol). After stirring at room temperature for 4 hours, the mixture was diluted with methanol (1 mL) and conc. aqueous HCl (1 mL). The mixture was stirred at 50 °C for 30 min. The mixture was filtered and purified by preparative RP-HPLC to give azetidin-3-yl(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)methanone as white solid. ^1H NMR (400 MHz, MeOD-d_4) δ 8.08 (s, 1H), 7.68 (d, 2H), 7.04 (d, 2H), 6.26 (s, 1H), 4.74-4.68 (m, 2H), 4.39-4.35 (m, 1H), 4.29-4.24 (m, 2H), 4.11 -4.07 (m, 1H), 3.74-3.71 (m, 1H), 3.25 -3.24 (m, 1H), 3.07-3.04 (m, 1H), 2.87-2.80 (m, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 1.87-1.84 (m, 2H), 1.66-1.56 (m, 2H); ESMS *m/z* 499.2 ($M + H^+$).

Example 17

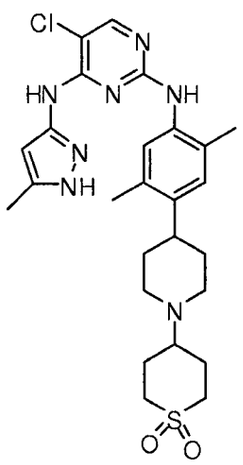
5-chloro-N^2-(2-fluoro-5-methyl-4-(1-(tetrahydro-1,1-dioxido-3-thienyl)piperidin-4-yl)phenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (145)



[0144] To 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (30 mg, 0.072 mml) in EtOH (0.5 mL) was added thiophene-2,3-dihydro-,1,1-dioxide (17 mg, 0.144 mmol). The resulting mixture was then heated to 130 °C for 2 hr.. After cooling down to room temperature, the mixture was concentrated and purified by preparative RP-HPLC to provide 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(tetrahydro-1,1-dioxido-3-thienyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine. ESMS m/z 534.2 ($M + H^+$).

Example 18

5-chloro-N^2-(2,5-dimethyl-4-(1-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl))piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (146)



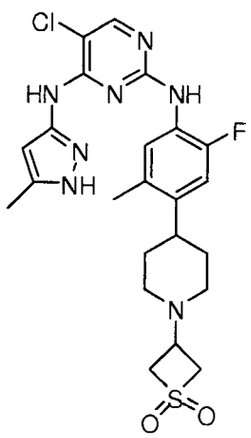
[0145] Step 1: To a solution of 5-chloro-N2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (30 mg, .073

mmol) in acetonitrile (1 mL) was added Cs_2CO_3 (47 mg, 0.15 mmol) and 4-iodotetrahydro-2H-thiopyran (48 mg, 0.22 mmol). This mixture was then stirred at 80 °C for 16 hr. After cooling down to room temperature, the mixture was treated with saturated aqueous NH_4Cl solution (3 mL) and extracted with EtOAc (3x3 mL). The organic layers were combined and concentrated. The residue was purified by silica gel chromatography (Gradient 0~8% MeOH/CH_2Cl_2 with NH_3) to provide 5-chloro-N2-(2,5-dimethyl-4-(1-(tetrahydro-2H-thiopyran-4-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as a white solid. ESMS m/z 512.2 ($M + H^+$).

[0146] Step 2: To 5-chloro-N2-(2,5-dimethyl-4-(1-(tetrahydro-2H-thiopyran-4-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (18 mg, .035 mmol) in CH_2Cl_2 (1 mL) was added m-CPBA (16 mg, .0.71 mmol) at 0 °C. The mixture was then warmed up to room temperature and stirred for 30 min; saturated aqueous $NaHCO_3$ solution (3 mL) was then added and the crude product extracted with CH_2Cl_2 (3 x3 mL). The combined organic layers were concentrated and purified by preparative thin layer chromatography (silica gel, 12 % MeOH/CH_2Cl_2 with NH_3) to provide 5-chloro-N2-(2,5-dimethyl-4-(1-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl))piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine. ESMS m/z 544.2 ($M + H^+$).

Example 19

5-chloro-N^2-(2-fluoro-5-methyl-4-(1-(1,1-dioxido-3-thietanyl)piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (148)

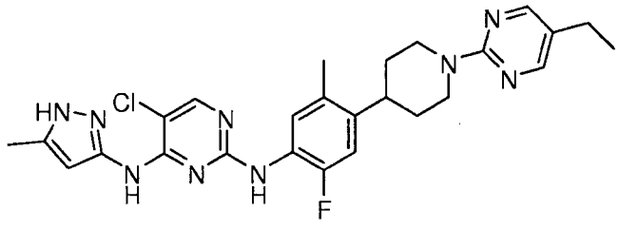


[0147] To 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (30 mg, 0.072 mmol) in MeOH (1

mL) was added 3-bromothietane 1,1-dioxide (15mg, 0.079 mmol) followed by TEA (15mg). The resulting mixture was stirred at room temperature for 5 hr and then concentrated. The resulting residue was purified by preparative RP-HPLC to provide 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(1,1-dioxido-3-thietanyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine. ^{1}H NMR (400 MHz, DMSO-d6 + 1 drop D2O) δ 8.02 (s, 1H), 7.37 (s, 1H), 7.02 (s, 1H), 6.23 (s, 1H), 4.28-4.22 (m, 2H), 4.12-4.07 (m, 2H), 3.22-3.18 (m, 1H), 2.95-2.92 (m, 2H), 2.68-2.62 (m, 1H), 2.22 (s, 3H), 2.13 (s, 3H), 2.07-2.01 (m, 2H), 1.71-1.55 (m, 4H). ESMS m/z 520.2 (M + H^+).

Example 20

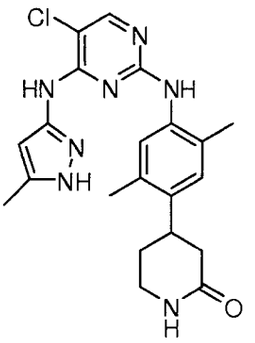
5-Chloro-N2-(4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (149)



[0148] To a mixture of 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (0.10 mmol) and triethylamine (83 uL, 0.6 mmol) in DMF (1.5 mL), was added 2-chloro-5-ethylpyrimidine (27 mg, 0.20 mmol). The mixture was heated in a microwave at 120 °C for 10 min. The reaction was filtered and the filtrate was purified by preparative RP-HPLC to afford 5-chloro-N2-(4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as a white solid. ESMS m/z 522.2 (M + H+).

Example 21

4-(4-(5-chloro-4-(5-methyl-*1H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-2-one (151)



[0149] Step 1: In a 5 mL microwave reaction tube was added 2-(2,5-dimethyl-4-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (143 mg, 0.516 mmol, prepared from 1-bromo-2,5-dimethyl-4-nitrobenzene by standard protocol), 1-(4-methoxybenzyl)-5,6-dihydropyridin-2(1H)-one (56 mg, 0.26 mmol, prepared by following a similar procedure as reported by Lerchner etc. in Chem. Eur. J. 2006, 12, 8208), chloro(1,5-cyclooctadiene)rhodium (I) dimer (13 mg, .026 mmol), KOH (0.13 mL 1N aqueous solution) and dioxane (1.2 mL). The tube was degassed, filled with N_2 and sealed. The reaction tube was then heated to 100 °C in a microwave reactor for 10 min. After the reaction tube was opened, the mixture was treated with saturated NH_4Cl aqueous solution (3 mL) and extracted with EtOAc (3 x 4 mL). The organic layers were combined and concentrated. The residue was purified by flash column chromatography (silica gel, gradient 0%~70% EtOAc/hexane), to provide 4-(2,5-dimethyl-4-nitrophenyl)-1-(4-methoxybenzyl)piperidin-2-one. ESMS m/z 369.2 (M + H^+).

[0150] Step 2: To 4-(2,5-dimethyl-4-nitrophenyl)-1-(4-methoxybenzyl)piperidin-2-one (63 mg, 0.17 mmol) in MeOH (10 mL) was added 10% w/w Pd/C (6 mg), the mixture was degassed and stirred under H_2 at room temperature for 14 hr. After removing the catalyst by filtration, the filtrate was concentrated to provide 4-(4-amino-2,5-dimethylphenyl)-1-(4-methoxybenzyl)piperidin-2-one as a pale yellowish oil. ESMS m/z 339.2 (M + H^+).

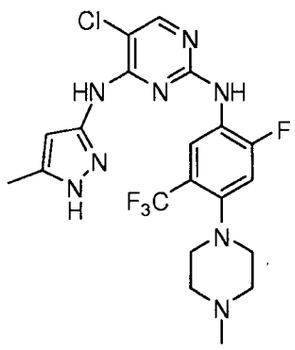
[0151] Step 3: To a mixture of 4-(4-amino-2,5-dimethylphenyl)-1-(4-methoxybenzyl)piperidin-2-one (23 mg, 0.094 mmol) and 2,5-dichloro-N-(5-methyl-1H-pyrazol-3-yl)pyrimidin-4-amine (29 mg, 0.086 mmol) in iPrOH (1 mL) was added HCl (60 uL, 4N in dioxane). The reaction vessel was then sealed and heated to 130 °C for 4 hr. After cooling to room temperature, the mixture was treated with saturated $NaHCO_3$ aqueous solution (3 mL) and extracted with EtOAc (3 x 4mL). The organic layers were combined and concentrated. The residue was purified by flash column

chromatography (silica gel, gradient 0~10% MeOH/CH_2Cl_2) to provide 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)-1-(4-methoxybenzyl)piperidin-2-one. ESMS m/z 546.2 ($M + H^+$).

[0152] Step 4: A solution of 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)-1-(4-methoxybenzyl)piperidin-2-one(45 mg) in TFA (0.5 mL) was heated to 100 °C for 24 hr. After cooling down to room temperature, the mixture was concentrated and purified by preparative RP-HPLC to provide 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-2-one. ESMS m/z 426.2 ($M + H^+$).

Example 22

5-chloro-N^2-(2-fluoro-4-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (157)



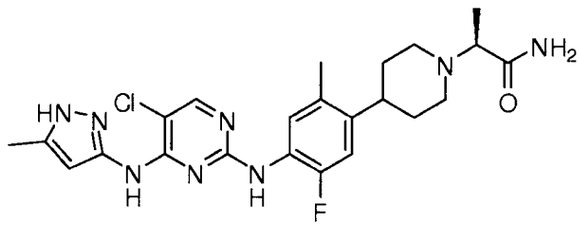
[0153] Step 1: To a microwave reaction tube was added 4-bromo-2-fluoro-5-(trifluoromethyl)aniline (256 mg, 1.0 mmol), 1-methylpiperazine (300mg, 3 mmol) $Pd_2(dba)_3$ (91.5 mg, 0.1 mmol), di-tert-butyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (60 mg, 0.2 mmol), NaOtBu (144mg, 1.5 mmol) and THF (3 mL). After the reaction tube was degassed and filled with N_2, the tube was heated to 120 °C in a microwave reactor for 40 min. The mixture was then poured into saturated NH_4Cl aqueous solution (10 mL) and extracted with EtOAc (3 x10 mL). The organic layers were combined and concentrated. The residue was purified by flash column chromatography (silica gel, gradient MeOH/CH_2Cl_2, 0~10%) to provide 2-fluoro-4-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)aniline as a white solid. ESMS m/z 278.1 ($M + H^+$).

[0154] Step 2: To a mixture of 2-fluoro-4-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)aniline (37 mg, 0.133 mmol) and 2,5-dichloro-N-(5-methyl-1H-

pyrazol-3-yl)pyrimidin-4-amine (36 mg, 0.147 mmol) in iPrOH (1 mL) was added HCl (100 uL, 4N in dioxane). The reaction vessel was then sealed and heated to 130 °C for 4 hr. After cooling to room temperature, the mixture was treated with saturated $NaHCO_3$ aqueous solution (5 mL) and extracted with EtOAc (3 x 5mL). The organic layers were combined and concentrated. The residue was purified by preparative thin layer chromatography (silica gel, 8% MeOH/CH_2Cl_2), to provide 5-chloro-N2-(2-fluoro-4-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine. ESMS m/z 485.2 ($M + H^+$).

Example 23

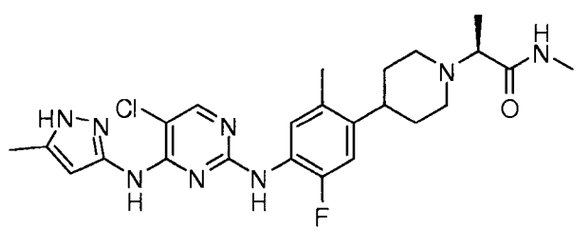
(*S*)-2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)propanamide (163)



[0155] A mixture of 5-chloro-N^2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (50.0 mg, 0.12 mmol), (*R*)-2-bromopropanamide (90.6 mg, 0.60 mmol), and triethylamine (102.0 μL, 0.60 mmol) in 2 mL of DMF was heated at 150°C in a microwave reactor for 30 min. The reaction mixture was directly purified by preparative RP-HPLC to afford (*S*)-2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)propanamide; ESMS *m/z* 487.2 ($M + H^+$).

Example 24

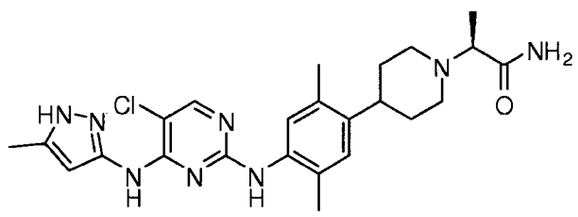
(*S*)-2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-N-methylpropanamide (164)



[0156] A mixture of 5-chloro-N^2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (50.0 mg, 0.12 mmol), (*R*)-2-bromo-*N*-methylpropanamide (100.0 mg, 0.60 mmol), and triethylamine (102.0 μL, 0.60 mmol) in 2 mL of DMF was heated at 150°C in a microwave reactor for 30 min. The reaction mixture was directly purified by preparative RP-HPLC to afford (*S*)-2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-N-methylpropanamide; ESMS *m/z* 501.2 ($M + H^+$).

Example 25

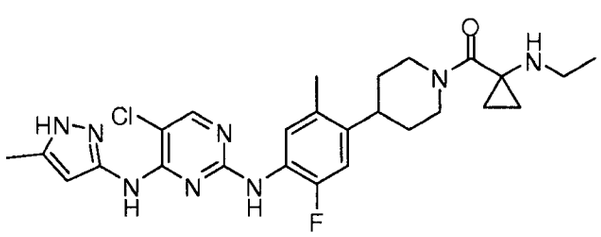
(S)-2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)propanamide (166)



[0157] A mixture of 5-chloro-N^2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (50.0 mg, 0.12 mmol), (*R*)-2-bromopropanamide (90.6 mg, 0.60 mmol), and triethylamine (102.0 μL, 0.60 mmol) in 2 mL of DMF was heated at 150°C in a microwave reactor for 30 min. The reaction mixture was directly purified by preparative RP-HPLC to afford (*S*)-2-(4-(4-(5-chloro-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)propanamide; ESMS *m/z* 483.2 ($M + H^+$).

Example 26

(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-(ethylamino)cyclopropyl)methanone (169)

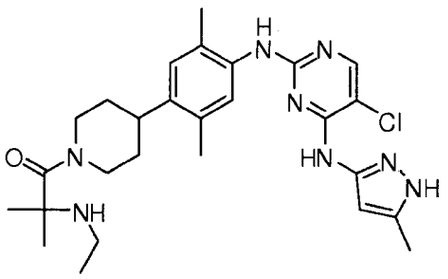


[0158] A mixture of 5-chloro-N^2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-

N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (67.3 mg, 0.17 mmol), 1-(*tert*-butoxycarbonyl(ethyl)amino)cyclopropanecarboxylic acid (38.0 mg, 0.17 mmol), HATU (63.0 mg, 0.17 mmol) and diisopropylethylamine (57 μL, 0.34 mmol) in 1 mL of DMF was stirred at room temperature overnight. The reaction mixture was partitioned between EtOAc and water, the combined organic extracts were dried (Na_2SO_4) and then concentrated *in vacuo*. The resulting crude mixture was dissolved in 5 mL of DCM and 4 mL of TFA and was then stirred for 2 h followed by concentration *in vacuo*. The crude product was purified by RP-HPLC to afford (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-(ethylamino)cyclopropyl)methanone; ESMS *m/z* 527.2 ($M + H^+$).

Example 27

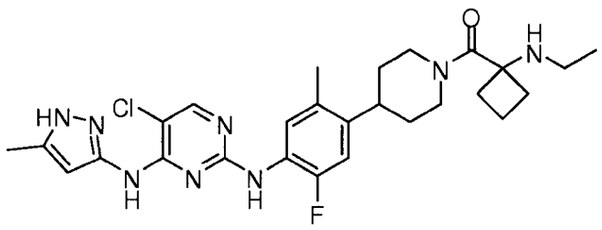
1-(4-(4-(5-chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(ethylamino)-2-methylpropan-1-one (175)



[0159] To a solution of 2-amino-1-(4-(4-(5-chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-methylpropan-1-one (6mg, 0.012 mmol) in acetone (0.5 mL) was added K_2CO_3 (11 mg, 0.079 mmol). The mixture was stirred at room temperature for 10 min. before the addition of EtI (6 mg, 0.038 mmol). The resulting mixture was then stirred at room temperature for 14 h before it was treated with saturated aqueous NH_4Cl (1 mL) and extracted with EtOAc (3 x 2mL). The organic layers were combined, concentrated, and the residue was purified by preparative thin layer chromatography (silica gel, 8% MeOH/DCM/NH_3) followed by further purification with preparative RP-HPLC to provide 1-(4-(4-(5-chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(ethylamino)-2-methylpropan-1-one; ESMS *m/z* 525.3 ($M + H^+$).

Example 28

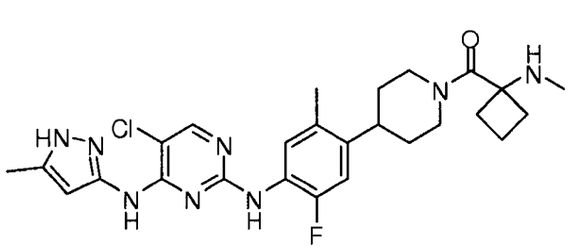
(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-(ethylamino)cyclobutyl)methanone (176)



[0160] A mixture of 5-chloro-N^2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (50.0 mg, 0.12 mmol), 1-(*tert*-butoxycarbonyl(ethyl)amino)cyclobutanecarboxylic acid (29.2 mg, 0.12 mmol), HATU (45.8 mg, 0.12 mmol) and di-isopropylethylamine (20 μL, 0.12 mmol) in 1 mL of DMF was stirred at room temperature overnight.. The reaction mixture was partitioned between EtOAc and water. The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo*. The resulting crude mixture was dissolved in 5 mL of DCM and 4 mL of TFA and was then stirred for 2 h followed by concentration *in vacuo*. The crude product was purified by RP-HPLC to afford (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-(ethylamino)cyclobutyl)methanone; ESMS *m/z* 541.3 ($M + H^+$).

Example 29

(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-(methylamino)cyclobutyl)methanone (177)

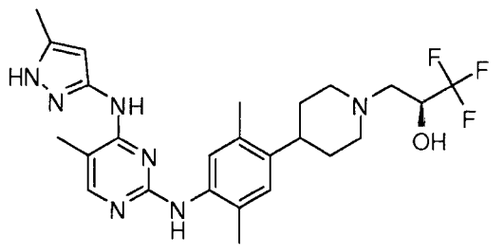


[0161] A mixture of 5-chloro-N^2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (50.0 mg, 0.12 mmol), 1-(*tert*-butoxycarbonyl(methyl)amino)cyclobutanecarboxylic acid (27.5 0.12 mmol), HATU

(45.8 mg, 0.12 mmol) and di-isopropylethylamine (20 μL, 0.12 mmol) in 1 mL of DMF was stirred at room temperature overnight. The reaction mixture was partitioned between EtOAc and water. The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo*. The resulting crude mixture was dissolved in 5 mL of DCM and 4 mL of TFA, and was stirred for 2 h followed by concentration *in vacuo*. The crude product was purified by RP-HPLC to afford (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-(mthylamino)cyclobutyl)methanone; ESMS *m/z* 527.2 ($M + H^+$).

Example 30

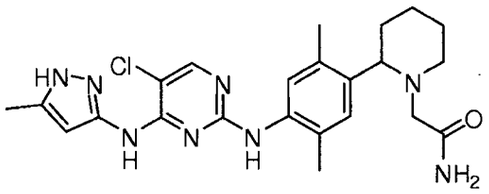
(*S*)-3-(4-(2,5-dimethyl-4-(5-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)phenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol (179)



[0162] To a solution of N^2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-5-methyl-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine hydrochloride (36.0 mg, 0.084 mmol) in DMF (0.5 mL) were added TEA (23.4 μL, 0.168 mmol) and (*S*)-2-(trifluoromethyl) oxirane (72.8 μL, 0.84 mmol). The reaction mixture was stirred at room temperature overnight, and purified by preparative RP-HPLC to provide (*S*)-3-(4-(2,5-dimethyl-4-(5-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)phenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol; ESMS *m/z* 504.3 ($M + H^+$).

Example 31

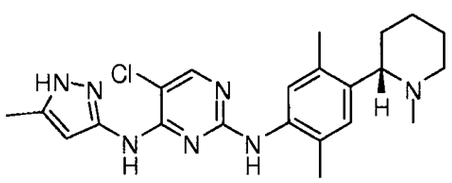
2-(2-(4-(5-Chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)acetamide (181)



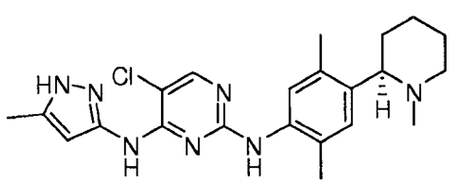
[0163] To a mixture of 5-Chloro-N2-(2,5-dimethyl-4-(piperidin-2-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (0.12 mmol) and triethylamine (83 uL, 0.6 mmol) in DMF (1.5 mL), was added 2-bromoacetamide (35 mg, 0.24 mmol). The mixture was stirred at room temperature for 3 h. The reaction was filtered and the filtrate was purified by RP-HPLC to afford 2-(2-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)acetamide as a white solid; ^{1}H NMR (400 MHz, MeOD-d4) 8.09 (s, 1H), 7.65 (d, 1H), 7.43 (s, 1H), 6.41 (s, 1H), 4.79-4.74 (m, 2H), 3.83-3.48 (m, 2H), 2.71 (s, 3H), 2.42 (s, 3H), 2.34 (s, 6H), 2.15-1.84 (m, 7H); ESMS *m/z* 469.2 (M + H$^+$).

Examples 32 and 33

(*S*) 5-Chloro-N2-(2,5-dimethyl-4-(1-methylpiperidin-2-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (183)



(*R*) 5-Chloro-N2-(2,5-dimethyl-4-(1-methylpiperidin-2-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (184)



[0164] Step 1: To a mixture of 1-bromo-2,5-dimethyl-4-nitrobenzene (185 mg, 1 mmol) and 2-(tributylstannyl)pyridine (202 mg, 1.1 mmol) in DMF (4 mL) was added tetrakis(triphenylphosphine) palladium (0) (58 mg, 0.05 mmol). The reaction tube was sealed, the mixture was purged with N_2 for 3 min and then heated at 120 °C under

N_2 for overnight. The reaction was cooled to room temperature and poured into saturated aqueous ammonia chloride solution. The crude reaction mixture was extracted with ethyl acetate (3 x 15 mL). The organic extracts were combined, washed with brine and concentrated. The crude product was purified with silica chromatography (60% ethyl acetate in hexanes) to afford 2-(2,5-dimethyl-4-nitrophenyl)pyridine as a white solid. The obtained solid was dissolved in acetic acid/TFA (15 mL/200 uL). To this solution was added PtO_2 (10% w/w). The reaction mixture was degassed and purged with H_2 for several times and then vigorously stirred under 1 atm. H_2 overnight. The mixture was filtered and the filtrate concentrated to afford 2,5-Dimethyl-4-(piperidin-2-yl)aniline as a yellow oil; ESMS *m/z* 205 ($M + H^+$).

[0165] Step 2: A mixture of 2,5-dichloro-N-(5-methyl-1H-pyrazol-3-yl)pyrimidin-4-amine (120 mg, 0.49 mmol) and 2,5-dimethyl-4-(piperidin-2-yl)aniline (100 mg, 0.49 mmol) in 2-propanol (10 mL) was treated with conc. aqueous HCl (7 drops). The mixture was sealed and heated in a microwave at 130 °C for 45 min. The mixture was concentrated to afford 5-Chloro-N2-(2,5-dimethyl-4-(piperidin-2-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine; ESMS *m/z* 412.1 ($M + H^+$). The crude product was used directly for the next step without further purification.

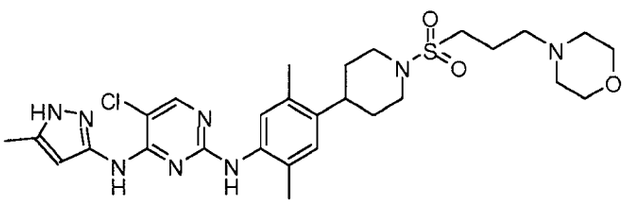
[0166] Step 3: To a solution of the crude product from the previous step in THF (1 mL) and methanol (1 mL) was sequentially added formaldehyde (100 uL, 1.3 mmol) and 5 drops of AcOH. The reaction mixture was stirred at room temperature for 1 h, then sodium cyanoborohydride (160 mg, 2.45 mmol) was added in one portion, and the reaction was stirred for an additional 30 min. The reaction was quenched by saturated aqueous NH_4Cl and concentrated *in vacuo* to give an oily residue. The residue was purified with RP-HPLC to afford (±)-5-Chloro-N2-(2,5-dimethyl-4-(1-methylpiperidin-2-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as a white solid; ESMS *m/z* 426.2 ($M + H^+$).

[0167] Step 4: Chiral separation of the racemic mixture was conducted with normal phase HPLC using ChiralPaK AD-H column using the following solvent system: hexanes (95%), EtOH (2.5%), MeOH (2.5%). The two purified enantiomer peaks were collected separately: (*R*)-5-Chloro-N2-(2,5-dimethyl-4-(1-methylpiperidin-2-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

and (*S*)-5-Chloro-N2-(2,5-dimethyl-4-(1-methylpiperidin-2-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine; both peaks: ESMS *m/z* 426.2 ($M + H^+$). The earlier eluting peak has been arbitrarily assigned as the (*R*) enantiomer.

Example 34

5-Chloro-N^2-(2,5-dimethyl-4-(1-(3-morpholinopropylsulfonyl)piperidin-4-yl)phenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (194)

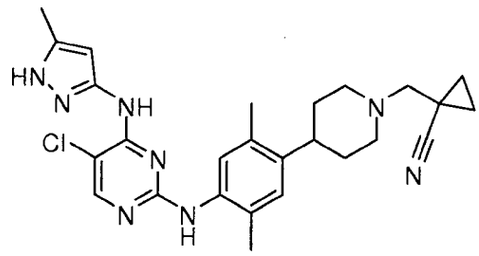


[0168] Step 1: To a solution of 5-chloro-N^2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (78 mg, 0.19 mmol) and TEA (0.52 mL, 3.78 mmol) in DCM (10 mL) was added 3-chloropropane-1-sulfonyl chloride (63 mg, 0.36 mmol, in 1 mL DCM). After stirring at rt for one hour, EtOAc (100 mL) was added. The mixture was sequentially washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica chromatography (0-100% EtOAc in hexanes gradient) to give 5-chloro-N2-(4-(1-(3-chloropropylsulfonyl)piperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as an off white solid; ESMS m/z 552.2 ($M+H^+$).

[0169] Step 2: The product from Step 1 was stirred in neat morpholine (0.5 mL) at 100 °C in a sealed vial for one hour. The reaction was purified by RP-HPLC to give 5-Chloro-N2-(2,5-dimethyl-4-(1-(3-morpholinopropylsulfonyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as a white powder; ESMS m/z 603.2 ($M+H^+$).

Example 35

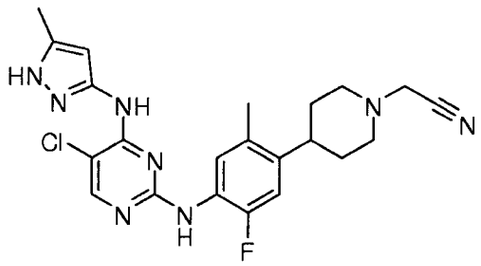
1-((4-(4-(5-chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)methyl)cyclopropanecarbonitrile (198)



[0170] To a solution of 5-chloro-N^2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (30 mg, 0.078 mmol) in acetonitrile (1.0 mL) was added (1-cyanocyclopropyl)methyl 4-methylbenzenesulfonate (16 mg, 0.10 mmol, prepared according to the procedure described in patent WO2005063247) followed by DIEA (30mg, 0.23 mmol) and KI (catalytic amount). The resulting mixture was heated to 70 °C for 14 h and then cooled down to room temperature. The resulting mixture was directly purified by preparative RP-HPLC to provide 1-((4-(4-(5-chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5dimethylphenyl)-piperidin-1-yl)methyl)cyclopropanecarbonitrile; ESMS *m/z* 491.2 ($M + H^+$).

Example 36

2-(4-(4-(5-chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)acetonitrile (199)

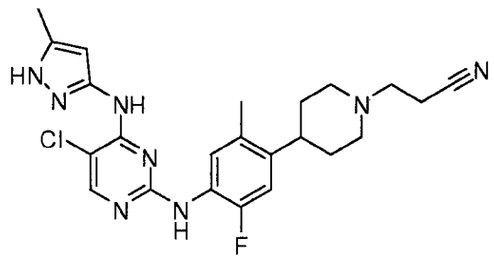


[0171] To a solution of 5-chloro-N^2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (20 mg, 0.048 mmol) in acetonitrile (0.5 mL) was added Cs_2CO_3 (31 mg, 0.096 mmol) and chloroacetonitrile (7 mg, 0.096 mmol). The resulting mixture was stirred at room temperature for 14 h before it was treated with saturated aqueous NH_4Cl (1 mL) and extracted with EtOAc (3 x 2mL). The organic layers were combined, concentrated, and the residue was purified by preparative RP-HPLC to provide 2-(4-(4-(5-chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-

yl)acetonitrile; ESMS *m/z* 455.2 ($M + H^+$).

Example 37

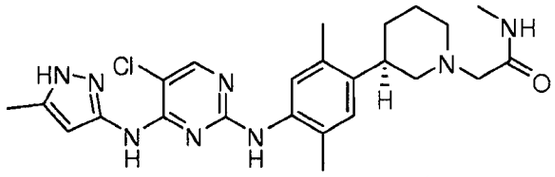
3-(4-(4-(5-chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)propanenitrile (200)



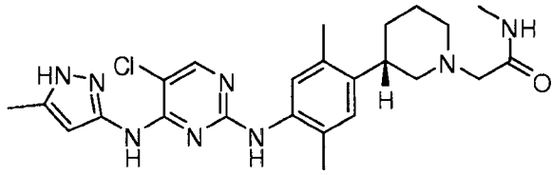
[0172] To a solution of 5-chloro-N^2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (20 mg, 0.048 mmol) in MeOH (0.5 mL) was added acrylonitrile (5 mg, 0.096 mmol). The resulting mixture was stirred at room temperature for 14 h and then purified directly by preparative RP-HPLC to provide 3-(4-(4-(5-chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)propanenitrile; ESMS *m/z* 469.2 ($M + H^+$).

Examples 38 and 39

(*R*)-2-(3-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide (207)



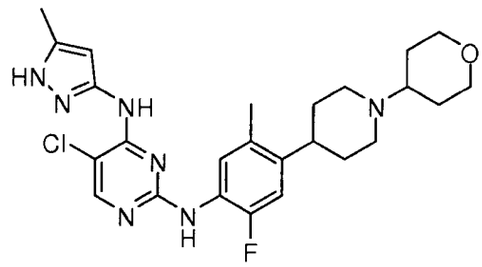
(*S*)-2-(3-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide (208)



[0173] A solution of 5-chloro-N^2-(2,5-dimethyl-4-(piperidin-3-yl)phenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (700 mg, 1.70 mmol), 2-bromo-*N*-methylacetamide (258mg, 1.70 mmol) and TEA (1.2 mL, 8.5 mmol) in DMF (4 mL) was stirred at rt for 30 min. The reaction was purified by RP-HPLC to give the product as a racemate; ESMS m/z 483.2 (M+1). Chiral separation of the racemic mixture was conducted with chiral HPLC (ChiralCel OD-H, Hex:EtOH:MeOH/80:10:10, 15 min run time, 1 mL/min). The two purified enantiomer peaks were collected separately, both as white solids: (*R*)-2-(3-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide and (*S*)-2-(3-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide; both peaks: ESMS *m/z* 483.2 ($M+H^+$). The earlier eluting peak (rt = 5.63 min. vs. rt = 7.62 min.) was arbitrarily assigned as the (*R*) enantiomer.

Example 40

5-chloro-N^2-(2-fluoro-5-methyl-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (209)

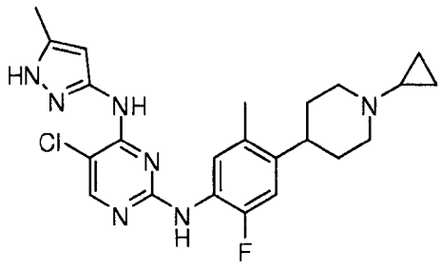


[0174] To a suspension of 5-chloro-N^2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (2.50 g, 6.0 mmol) in a mixed solvent of MeOH (42 mL) and DCM (10 mL) was added dihydro-2H-pyran-4(3H)-one (3.33 mL, 36.0 mmol) and TEA (8.36 mL, 60.0 mmol). The reaction mixture was heated at 60 °C for 1 h before $NaCNBH_3$ (1.66 g, 26.4 mmol) was added. The mixture was heated at 60 °C for another 2 h, cooled down to room temperature, diluted with DCM (60 mL), dry loaded onto silica gel (12.5 g), and purified by silica gel chromatography (DCM with 1% NH_3 to 10% MeOH in DCM with 1% NH_3 gradient) to provide 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as a white solid; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.08 (br, 1H), 9.58 (br, 1H), 8.65 (d, *J*

= 28.4 Hz, 1H), 8.02 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 12.4 Hz, 1H), 6.08 (br, 1H), 3.89 (dd, J = 10.8, 3.6 Hz, 2H), 3.28 (t, J = 10.4 Hz, 2H), 2.99 (d, J = 10.8 Hz, 2H), 2.64-2.43 (m, 2H), 2.24-2.15 (m, 8H), 1.71-1.40 (m, 8H); ESMS *m/z* 500.2 ($M + H^+$).

Example 41

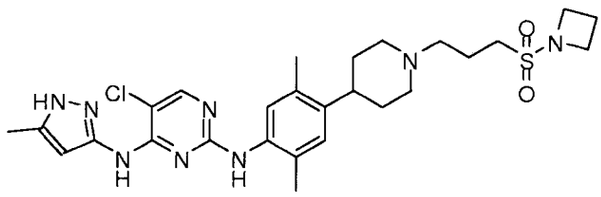
5-chloro-N^2-(4-(1-cyclopropylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (210)



[0175] To a solution of 5-chloro-N^2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (30 mg, 0.072 mmol) in MeOH (0.7 mL) was added AcOH (35 mg, 0.58 mmol), (1-ethoxycyclopropoxy)trimethylsilane (37 mg, 0.216 mmol) and a small amount of 4Å molecular sieves. The mixture was stirred at room temperature for 1 h before the addition of $Na(CN)BH_3$ (14 mg, 0.216 mmol). The resulting mixture was then stirred at 60 °C for 14 h and cooled to room temperature. Saturated aqueous NH_4Cl (2 mL) was added and the mixture was extracted with EtOAc (3 x 3 mL). The combined organic layers were concentrated and purified by preparative RP-HPLC to provide 5-chloro-N^2-(4-(1-cyclopropylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine; ^{1}H NMR (400 MHz, MeOD-d4) δ 7.97 (s, 1H), 7.84 (d, 1H), 7.50 (s, 1H), 6.93 (d, 1H), 6.29 (s, 1H), 5.33 (s, 1H), 2.80 (m, 1H), 2.58 (s, 2H), 2.28 (s, 3H), 2.24 (s, 3H), 1.96 (m, 1H), 1.80-1.85(m, 2H), 1.65-1.75 (m, 2H), 0.2-0.7 (m, 6H); ESMS *m/z* 456.2 ($M + H^+$).

Example 42

N^2-(4-(1-(3-(azetidin-1-ylsulfonyl)propyl)piperidin-4-yl)-2,5-dimethylphenyl)-5-chloro-*N*^{4}-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (214)

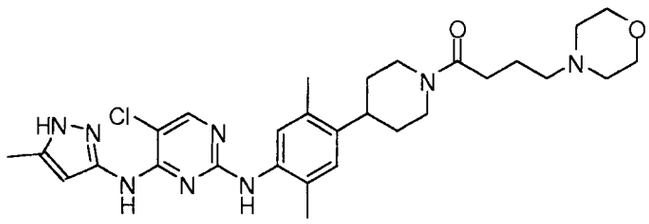


[0176] Step 1: To a solution of azetidine (12 mg, 0.21 mmol) and TEA (0.1 mL, 0.71 mmol) in DCM (5 mL) was slowly added a solution of 3-chloropropane-1-sulfonyl chloride (34 mg, 0.19 mmol) in DCM (1 mL). After stirring at rt overnight, the solvent was removed *in vacuo*. The resulting 1-(3-chloropropylsulfonyl)azetidine crude product was dissolved in NMP (1.9 mL, 0.1 mmol/mL) and used in the next step without further purification; ESMS m/z 198.0 ($M+H^+$).

[0177] Step 2: A mixture of 5-chloro-N^2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (42 mg, 0.1 mmol), 1-(3-chloropropylsulfonyl) azetidine (Step 1, 0.1 mmol), TEA (70 μL) and sodium iodide (150 mg) in NMP (1 mL) was placed in a sealed vial which was heated in a microwave for 30 min at 150 °C. The reaction was purified by RP-HPLC to give N2-(4-(1-(3-(azetidin-1-ylsulfonyl)propyl)piperidin-4-yl)-2,5-dimethylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as a white powder; ESMS m/z 573.3 ($M+H^+$).

Example 43

1-(4-(4-(5-Chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-4-morpholinobutan-1-one (224)



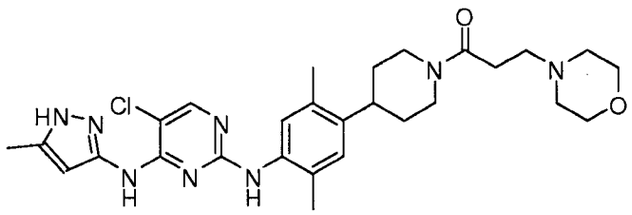
[0178] Step 1: To a solution of HATU (95 mg, 0.255 mmol) and 4-chlorobutanoic acid (36 mg, 0.25 mmol) in DMF (1 mL) was added DIEA (0.1 mL). After stirring at rt for 3 min, 5-chloro-N^2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (100 mg, 0.24 mmol) in DMF (2 mL) was added. The reaction was stirred at rt for 90 min. at which point LCMS indicates the reaction was complete and that 4-chloro-1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-

ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)butan-1-one has been generated; ESMS m/z 516.1($M+H^+$).

[0179] Step 2: Morpholine (0.5 mL) was added directly to the crude reaction mixture from Step 1 (1 mL). The resulting solution was stirred at 100 °C in a sealed vial for 1.5 h. The crude product was purified by RP-HPLC to give 1-(4-(4-(5-Chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-4-morpholinobutan-1-one as a white powder; ESMS m/z 567.3 ($M+H^+$).

Example 44

1-(4-(4-(5-Chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-3-morpholinopropan-1-one (225)



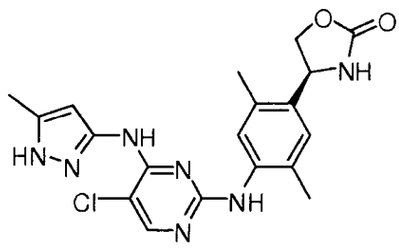
[0180] Step 1: A solution of HATU (108 mg, 0.28 mmol), 3-chloropropanoic acid (30 mg, 0.28 mmol) and DIEA (0.1 mL) in DMF (1 mL) was stirred at rt. After 3 min, this solution was transferred to a solution of 5-chloro-N^2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine solution (111 mg, 0.27 mmol) in DMF (10 mL). The resulting mixture was stirred at rt overnight. The reaction was quenched with water (20 mL) and extracted with EtOAc (3x30 mL). The combined EtOAc layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica chromatography (0-10% MeOH in DCM gradient with 1% NH_3 additive) to give 1-(4-(4-(5-chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)prop-2-en-1-one as a light brown oil; ESMS m/z 466.1 ($M+H^+$).

[0181] Step 2: A solution of 1-(4-(4-(5-chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)prop-2-en-1-one (41 mg, 0.88 mmol) and morpholine (0.1 mL) in DMF (1 mL) was stirred at rt overnight. The crude product was purified by RP-HPLC to give 1-(4-(4-(5-Chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-

dimethylphenyl)piperidin-1-yl)-3-morpholinopropan-1-one as a white powder; ESMS m/z 553.2 ($M+H^+$).

Example 45

(S)-4-(4-(5-chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)oxazolidin-2-one (230)



[0182] Step 1: To a microwave reaction vessel was added a mixture of 1-bromo-2,5-dimethyl-4-nitrobenzene (1.15 g, 5.0 mmol), dibutyl vinylboronate (1.16 g, 6.3 mmol) , $Pd(PPh_3)_4$ (289 mg, 0.25 mmol), CsF (2.28g, 15 mmol) and a mixed solvent (1,2-dimethoxyethane/MeOH=2:1, 15 mL). The mixture was degassed and sealed with N_2. The reaction vessel was then heated to 130 °C in a microwave reactor for 15 min. After opening the reaction vessel, the mixture was poured into saturated NH_4Cl aqueous solution (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). After removing the drying agent by filtration, the filtrate was concentrated and purified by flash column chromatography (silica gel, 0-30% EtOAc in hexanes gradient) to provide 1,4-dimethyl-2-nitro-5-vinylbenzene as needlelike crystals; ESMS *m/z* 178.1 ($M + H^+$).

[0183] Step 2: 1,4-dimethyl-2-nitro-5-vinylbenzene was reacted via the asymmetric synthetic method reported by N. Barta *et al.* (*Org. Lett.* **2000**, *2*, 2821) followed by purification with preparative RP-HPLC to provide (*S*)-4-(2,5-dimethyl-4-nitrophenyl)oxazolidin-2-one; ESMS *m/z* 237.1 ($M + H^+$).

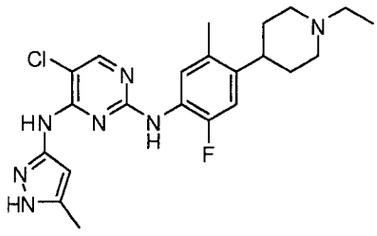
[0184] Step 3: To a solution of (*S*)-4-(2,5-dimethyl-4-nitrophenyl)oxazolidin-2-one (55 mg, 0.23 mmol) in MeOH (5 mL) was added Pd/C (5mg, 10% w/w). The mixture was degassed and stirred at room temperature under 1 atm. H_2 for 14 h. The Pd/C was removed by filtering through Celite. The filtrate was concentrated to provide (*S*)-4-(4-amino-2,5-dimethylphenyl)-oxazolidin-2-one which was used in the next step without further purification; ESMS *m/z* 207.1 ($M + H^+$).

[0185] Step 4: To a reaction tube was added (*S*)-4-(4-amino-2,5-

dimethylphenyl)oxazolidin-2-one (48 mg, 0.23 mmol), 2,5-dichloro-N-(5-methyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (77 mg, 0.32 mmol), ^{i}PrOH (2 mL) and HCl (0.13 mL, 0.52 mmol, 4N in dioxane). The tube was then sealed and heated at 130 °C for 6 h. After cooling down to room temperature, the mixture was concentrated and purified by preparative RP-HPLC to provide (*S*)-4-(4-(5-chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethyl-phenyl)oxazolidin-2-one; ESMS *m/z* 414.1 (M + H^+).

Example 46

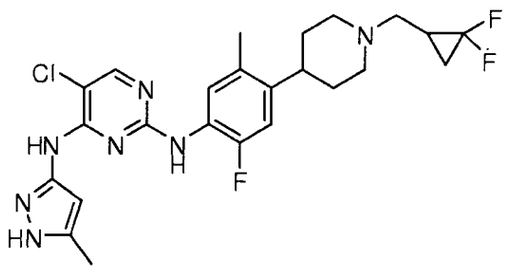
5-chloro-N^2-(4-(1-ethylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (232)



[0186] A mixture of 5-chloro-N^2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (400 mg, 0.96 mmol), iodoethane (92.5 μL, 1.2 mmol) and triethylamine (201.5 μL, 1.4 mmol) in 4 mL of DMF was heated at 60°C for 2 h. The reaction mixture was partitioned between EtOAc and water. The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (MeOH/DCM: 1/9) to afford 5-chloro-N^2-(4-(1-ethylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine; ^{1}HNMR (DMSO-d_6) δ 8.01 (s, 1H), 7.35 (m, 1H), 7.02 (d, 1H), 6.22 (s,1H), 2.97 (d, 2H), 2.62 (m, 1H), 2.34 (q, 2H), 2.21 (s, 3H), 2.13 (s, 3H), 1.98 (t, 2H), 1.64 (m, 4H), 1.01 (t, 3H); ESMS *m/z* 444.2 (M + H^+).

Example 47

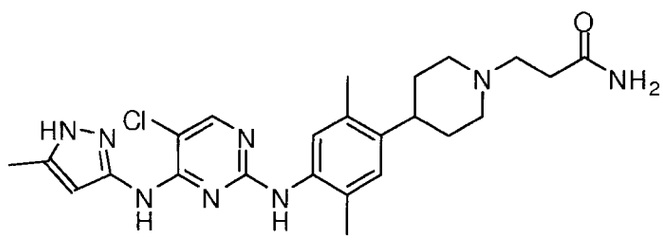
5-chloro-N^2-(4-(1-((2,2-difluorocyclopropyl)methyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (235)



[0187] A mixture of 5-chloro-N^2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (40 mg, 0.096 mmol), 2-(bromomethyl)-1,1-difluorocyclopropane (32.8 mg, 0.19 mmol) and triethylamine (20.2 μL, 0.14 mmol) in 1 mL of DMF was heated at 150°C in a microwave reactor for 30 min. The crude product was purified by RP-HPLC to afford 5-chloro-N^2-(4-(1-((2,2-difluorocyclopropyl)methyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine; ESMS *m/z* 506.2 ($M + H^+$).

Example 48

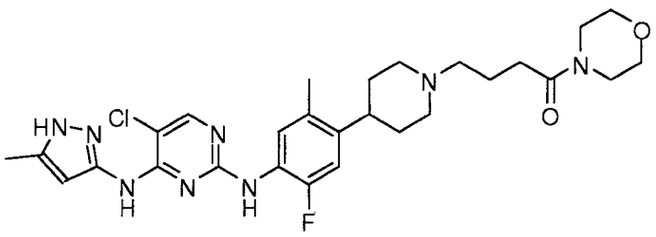
3-(4-(4-(5-Chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)propanamide (236)



[0188] A solution of 5-chloro-N^2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-*1H*-pyrazol-3-yl)pyrimidine-2,4-diamine (41 mg, 0.1 mmol), acrylamide (24 mg, 0.33 mmol) and DIEA (87 μL, 0.5 mmol) in NMP (1 mL) was stirred at 80 °C for 10 h. LCMS at this point shows the reaction was not complete, so additional acrylamide (2x36mg) was added and the reaction continued until LCMS shows the reaction was complete. The crude product was purified by RP-HPLC to give 3-(4-(4-(5-Chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)propanamide as a white powder; ESMS m/z 483.2 (M+1).

Example 49

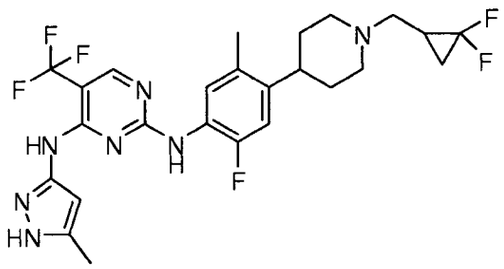
4-(4-(4-(5-Chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-1-morpholinobutan-1-one (246)



[0189] A mixture of 5-chloro-N^2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (41 mg, 0.1 mmol), 4-chloro-1-morpholinobutan-1-one (29 mg, 0.15 mmol) and DIEA (0.1 mL, 0.58 mmol) in NMP (1 mL) was stirred at 80 °C. After 10 h, additional 4-chloro-1-morpholinobutan-1-one (51 mg) was added, and the reaction continued overnight. The crude product was purified by RP-HPLC to give 4-(4-(4-(5-Chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-1-morpholinobutan-1-one as a white powder; ESMS m/z 571.3.3 ($M+H^+$).

Example 50

N^2-(4-(1-((2,2-difluorocyclopropyl)methyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine (251)

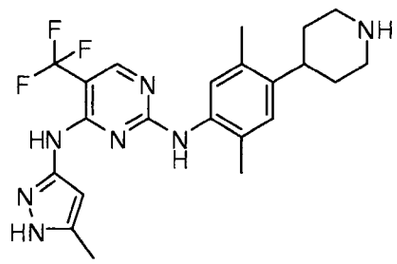


[0190] A mixture of N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine (100 mg, 0.22 mmol), 2-(bromomethyl)-1,1-difluorocyclopropane (76.4 mg, 0.45 mmol) and triethylamine (60.6 μL, 0.42 mmol) in 1 mL of DMF was heated at 60°C in a microwave reactor for 2 h. The crude product was purified by RP-HPLC to afford N^2-(4-(1-((2,2-difluorocyclopropyl)methyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine; ESMS

m/z 540.2 ($M + H^+$).

Example 51

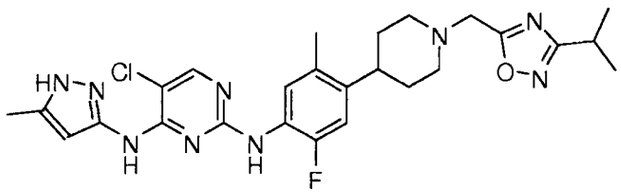
N^{2-}(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine (257)



[0191] A mixture of 2-chloro-N-(5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-4-amine (513.0 mg, 0.9 mmol), tert-butyl-4-(4-amino-2,5-dimethylphenyl)piperidine-1-carboxylate (282.7 mg, 0.9 mmol), and concentrated aqueous HCl (10 drops) in *i*-PrOH (12 mL) was heated at 150°C in a microwave reactor for 30 min. The crude product was purified by RP-HPLC to afford N^{2-}(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine; ESMS *m/z* 446.2 ($M + H^+$).

Example 52

5-Chloro-N^2-(2-fluoro-4-(1-((3-isopropyl-1,2,4-oxadiazol-5-yl)methyl)piperidin-4-yl)-5-methylphenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (259)

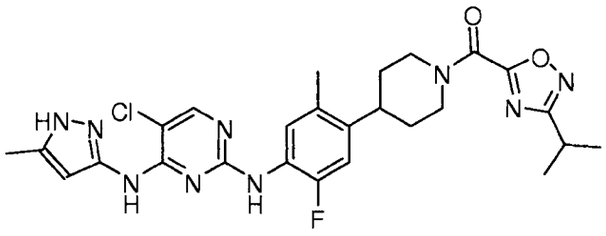


[0192] A mixture of 5-chloro-N^2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (42 mg, 0.1 mmol), 5-(chloromethyl)-3-isopropyl-1,2,4-oxadiazole (17 mg, 0.10 mmol) and DIEA (86 μL, 0.5 mmol) in DMF (1 mL) was stirred at rt overnight. The reaction was diluted with EtOAc (50 mL) and washed with water (2x5mL). The EtOAc layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica

chromatography (50-100% EtOAc in hexanes gradient) to give 5-Chloro-N2-(2-fluoro-4-(1-((3-isopropyl-1,2,4-oxadiazol-5-yl)methyl)piperidin-4-yl)-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as a white solid; ESMS m/z 540.2 ($M+H^+$).

Example 53

(4-(4-(5-Chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(3-isopropyl-1,2,4-oxadiazol-5-yl)methanone (265)



[0193] Step 1: A solution of isobutyronitrile (4.49 mL, 50 mmol) and hydroxylamine (12.3 mL, 200 mmol) in anhydrous ethanol (20 mL) was stirred at 60 °C for two days. The solvent was evaporated. The residue was coevaporated repeatedly with toluene to give (*E*)-*N'*-hydroxyisobutyrimidamide as a light yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (br s, 1H), 4.52 (br s, 2H), 2.43 (septet, J = 6.8 Hz, 1H), 1.15 (d, J = 6.8 Hz, 6H).

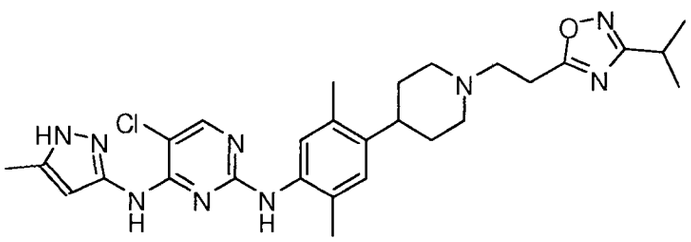
[0194] Step 2: A solution of (*E*)-*N'*-hydroxyisobutyrimidamide (0.51g, 5 mmol) and trichloroacetic anhydride (2.31 g, 7.5 mmol) in toluene (20 mL) was stirred at 80 °C. After 4 h, the reaction was diluted with EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$ (2x10 mL), dried over Na_2SO_4 and evaporated to give 3-Isopropyl-5-(trichloromethyl)-1,2,4-oxadiazole as a clear liquid which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.16 (septet, J = 7.2 Hz, 1H), 1.39 (d, J = 6.8 Hz, 6H).

[0195] Step 3: A mixture of 5-chloro-N^2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (42 mg, 0.1 mmol), 3-isopropyl-5-(trichloromethyl)-1,2,4-oxadiazole (46 mg, 0.2 mmol) and DIEA (40 μL, 0.23 mmol) in MeOH (1 mL) was stirred at 70 °C overnight. The crude reaction mixture was purified by RP-HPLC to give (4-(4-(5-Chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(3-

isopropyl-1,2,4-oxadiazol-5-yl)methanone as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (br s, 2H), 8.50 (s, 1H), 8.07 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 12.4 Hz, 1H), 6.16 (s, 1H), 5.53 (s, 1H), 3.98 (d, J = 13.2 Hz, 1H), 3.34 (dt, J = 2.0, 2.8 Hz, 1H), 3.15 (m, 1H), 2.82 (m, 2H), 2.62 (t, J = 4.8 Hz, 2H), 2.34 (s, 3H), 2.25 9s, 3H), 1.90 (m, 2H), 1.76 (2 H); ESMS *m/z* 554.2 ($M+H^+$).

Example 54

5-Chloro-N_2-(4-(1-(2-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl)piperidin-4-yl)-2,5-dimethylphenyl)-N_4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (269)

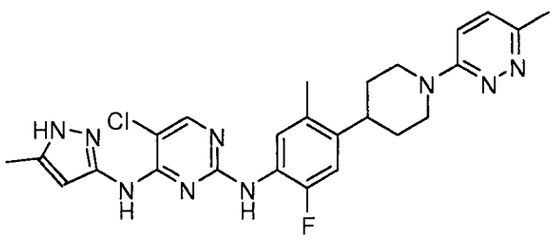


[0196] Step 1: A mixture of (*E*)-*N'*-hydroxyisobutyrimidamide (510 mg, 5 mmol), 3-chloropropanoic acid (542 mg, 5 mmol) and dicyclohexylcarbodiimide (1.24 g, 6 mmol) in anhydrous dioxane (20 mL) was stirred at 0 °C for 1 h and then at room temperature for an additional 1 h. The reaction was then heated at 80 °C for an additional 18 h. The reaction was filtered and the filtrate was evaporated. The resulting residue was purified by silica chromatography (0-100% EtOAc in hexanes gradient) to give 5-(2-chloroethyl)-3-isopropyl-1,2,4-oxadiazole; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (t, J = 7.2 Hz, 2H), 3.27 (t, J = 7.2 Hz, 2H), 3.03 (septet, J = 7.2 Hz, 1H), 1.13 (d, J = 7.2 Hz, 6H); ESMS *m/z* 175.1 ($M+H^+$).

[0197] Step 2: A mixture of 5-chloro-N_2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-N_4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (14 mg, 0.033 mmol), 5-(2-chloroethyl)-3-isopropyl-1,2,4-oxadiazole (9 mg, 0.053 mmol) and DIEA (29 uL, 0.17 mmol) in NMP (1 mL) was stirred at 50 °C for 3 days. The crude reaction mixture was purified by RP-HPLC to give 5-Chloro-N2-(4-(1-(2-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl)piperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as a white solid; ESMS *m/z* 550.3 ($M+H^+$).

Example 55

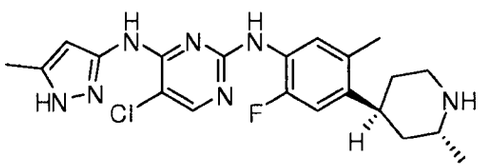
5-Chloro-N_2-(2-fluoro-5-methyl-4-(1-(6-methylpyridazin-3-yl)piperidin-4-yl)phenyl)-N_4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (277)



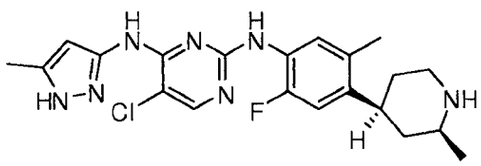
[0198] A suspension of 5-chloro-N^2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (20 mg, 0.05 mmol), 3-chloro-6-methylpyridazine (13 mg, 0.1 mmol) and Cs_2CO_3 (33 mg, 0.1 mmol) in dioxane (1 mL) was stirred at 150 °C in a sealed vial. After 15 h, additional 3-chloro-6-methylpyridazine (26 mg) and Cs_2CO_3 (66 mg) were added. The reaction was continued for an additional 3 h. The crude reaction mixture was purified by RP-HPLC to give 5-Chloro-N2-(2-fluoro-5-methyl-4-(1-(6-methylpyridazin-3-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as a white solid; ESMS *m/z* 508.2 ($M+H^+$).

Examples 56 and 57

5-chloro-N2-(2-fluoro-5-methyl-4-((*trans*)-2-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (279)



5-chloro-N2-(2-fluoro-5-methyl-4-((*cis*)-2-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (280)



[0199] Step 1: A solution of *tert*-butyl-2-methyl-4-oxopiperidine-1-carboxylate (1 g, 4.69 mmol) in THF (20 mL) was added dropwise into a cooled (-78 °C), vigorously stirring solution of LDA (3.75 mL of 1.5 M solution in cyclohexanes, 5.63 mmol) in THF (20 mL), under N_2. The reaction mixture was stirred at -78 °C for 30 min before adding a solution of phenyl trifluorosulfonimide (1.84 g, 5.16 mmol) in THF (20 mL). Following this addition, the reaction mixture was warmed to room temperature and stirred for 3 h. The reaction was cooled to 0 °C and quenched with 100 mL of saturated aqueous NH_4Cl, followed by filtration through Celite. The filtrate was added to 100 mL of EtOAc and the layers were separated. The organic layer was washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified by silica chromatography (0-30% EtOAc in hexanes gradient and checked by TLC stained with 2% of $KMnO_4$ in EtOH) to afford *tert*-butyl 2-methyl-4-(trifluoromethylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate as a yellow solid.

[0200] Step 2: To a mixture of 2-fluoro-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (587 mg, 2.33 mmol), *tert*-butyl 2-methyl-4-(trifluoromethylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (968 mg, 2.80 mmol) and sodium carbonate (1.73 g, 16.35 mmol) in DMF/H_2O (20/5 mL) was added tetrakis(triphenylphosphine) palladium (0) (135 mg, 5% mmol). The reaction tube was sealed, the mixture was purged with N_2 for 3 min and then heated at 100°C under N_2 for 8 h. The reaction was cooled to room temperature and poured into saturated aqueous ammonia chloride solution. The crude reaction mixture was extracted with ethyl acetate (3 x 15 mL). The organic extracts were combined, washed with brine and concentrated. The crude product was purified with silica chromatography (50% ethyl acetate in hexanes) to afford *tert*-butyl 4-(4-amino-5-fluoro-2-methylphenyl)-6-methyl-5,6-dihydropyridine-1(2H)-carboxylate as a yellow oil. The obtained oil was dissolved in methanol (20 mL). To the solution was added Pd/C (10%). The reaction mixture was degassed and purged with H_2 for several times and stirred vigorously under 1 atm. H_2 overnight. The mixture was filtered and the filtrate concentrated to afford *tert*-butyl 4-(4-amino-5-fluoro-2-methylphenyl)-2-methylpiperidine-1-carboxylate as a white solid. ESMS *m/z* 267 (M -56+ H^+).

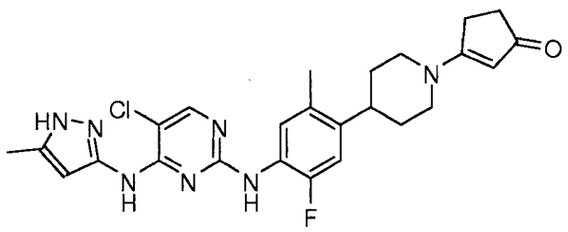
[0201] Step 3: A mixture of 2,5-dichloro-*N*-(5-methyl-1H-pyrazol-3-yl)pyrimidin-4-amine (346 mg, 1.42 mmol) and *tert*-butyl 4-(4-amino-5-fluoro-2-methylphenyl)-2-

methylpiperidine-1-carboxylate (352 mg, 1.09 mmol) in 2-propanol (10 mL) was treated with conc. HCl (12N, 0.43 mL). The mixture was sealed and heated in a microwave at 130 °C for 45 min. The mixture was concentrated. The residue was purified by RP-HPLC to afford 5-Chloro-N2-(2-fluoro-5-methyl-4-(2-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as a white solid. ESMS *m/z* 430.1 ($M + H^+$).

[0202] Step 4: 5-Chloro-N2-(2-fluoro-5-methyl-4-(2-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (20 mg, 0.046 mmol) was dissolved in a solvent mixture of DCM and methanol (0.5 mL, 10/1 v/v + 0.175N NH_3). The mixture was applied to preparative TLC in order to separate the *cis* and *trans* stereoisomers (eluent: 6% MeOH in DCM with 0.1N NH_3) of 5-Chloro-N2-(2-fluoro-5-methyl-4-(2-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as white solids. The *trans* isomer was the preparative TLC top band and the *cis* isomer was the preparative TLC bottom band; ESMS *m/z* 430.1 ($M + H^+$); *cis* stereoisomer ^1H NMR (400 MHz, MeOD-d4): δ 8.03 (s, 1H), 7.84 (d, 1H), 7.02 (d, 1H), 6.24 (d, 1H), 3.90-3.85 (m, 1H), 2.32 (s, 3H), 2.27 (s, 3H), 2.03-1.84 (m, 2H), 1.65-1.54 (m, 1H), 1.55 (d, 3H), 1.38-1.19 (m, 4H).

Example 58

3-(4-(4-(5-Chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)cyclopent-2-en-one (282)

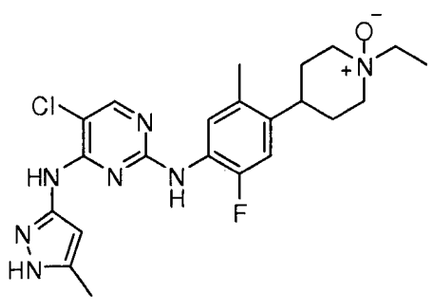


[0203] A mixture of 5-chloro-N^2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (43 mg, 0.1 mmol), cyclopentane-1,3-dione (89 mg, 9.1 mmol), sodium cyanoborohydride (19 mg, 0.3 mmol) and DIEA (0.2 mL, 11 mmol) in MeOH (1 mL) was stirred in a sealed vial at 60 °C. After 2.5 h, additional sodium cyanoborohydride (19 mg, 0.3 mmol) was added and the reaction continued to stir at 60 °C overnight. The mixture was purified by RP-HPLC to give 3-(4-(4-(5-Chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-

ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)cyclopent-2-en-one as an off white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (br s, 1H), 9.83 (br s, 1H), 8.90 (s, 1H), 8.32 (d, J = 6.8 Hz, 1H), 7.88 (d, J = 12.8 Hz, 1H), 6.97 (s, 1H), 6.04 (s, 1H), 5.30 (br s, 1H), 4.71 (d, J = 12.0 Hz, 2H), 4.04 (t, J = 12.4 Hz, 2H), 3.84 (m, 1H), 3.53 (m, 2H), 3.13 (m, 2H), 3.08 (s, 3H), 2.96 (s, 3H), 2.59-2.40 (m, 4H); ESMS *m/z* 496.2 ($M+H^+$).

Example 59

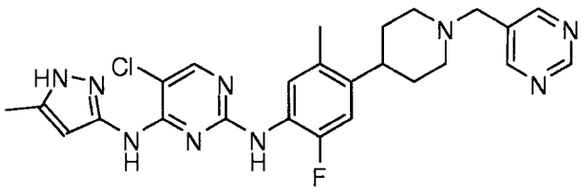
4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)-1-ethylpiperidine-1-oxide (289)



[0204] To a solution of 5-chloro-N^2-(4-(1-ethylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (22.2 mg, 0.05 mmol) in DCM (10 mL) and MeOH (1 mL) was added MCPBA (11.2 mg, 0.07 mmol). The reaction was stirred at room temperature overnight. The reaction mixture was partitioned between DCM and saturated aqueous $NaHCO_3$, the combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by RP-HPLC to afford 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)-1-ethylpiperidine-1-oxide; ^{1}HNMR (MeOD-d_4) δ7.91 (s, 1H), 7.69 (d, 1H), 7.00 (d, 1H), 6.15 (s, 1H), 3.28 (m, 4H), 2.91 (m, 1H), 2.32 (m, 2H), 2.20 (s, 3H), 2.16 (s, 3H), 1.83 (s, 2H), 1.64 (d, 2H), 1.31 (t, 3H).; ESMS *m/z* 460.2 ($M + H^+$).

Example 60

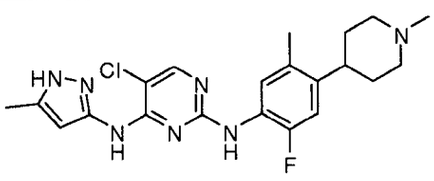
5-Chloro-N^2-(2-fluoro-5-methyl-4-(1-(pyrimidin-5-ylmethyl)piperidin-4-yl)phenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (314)

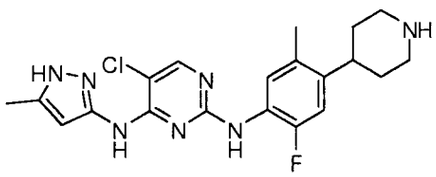
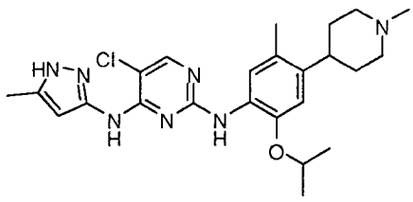
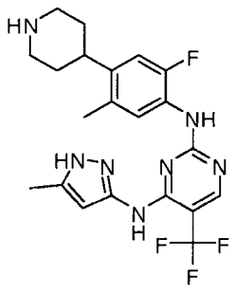
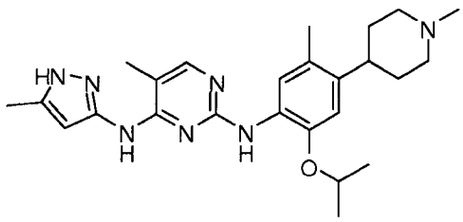


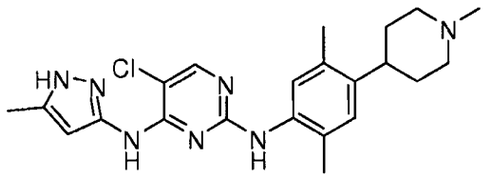
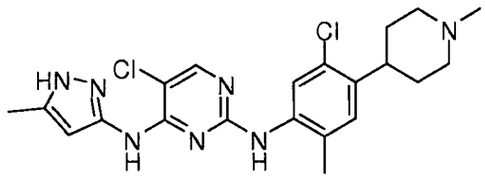
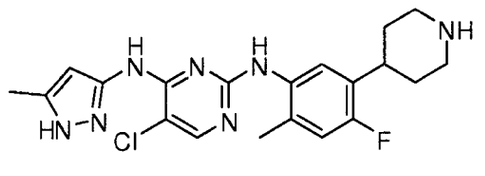
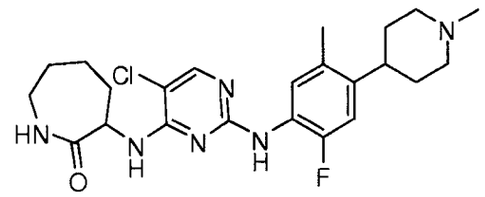
[0205] To a solution of 5-chloro-N^2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (45 mg, 0.1 mmol) and pyrimidine-5-carbaldehyde (32 mg, 0.3 mmol) in DCM (1.5 mL) was added $NaBH(OAc)_3$ (64 mg, 0.3 mmol), followed by addition of AcOH (12 uL). After stirring at room temperature in a sealed vial for 16 h, the reaction was quenched with EtOAc (50 mL). The reaction mixture was sequentially washed with water (10 mL), brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica chromatography (0-10% MeOH in EtOAc gradient with 1% NH_3 in MeOH additive) to give 5-Chloro-N2-(2-fluoro-5-methyl-4-(1-(pyrimidin-5-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine as an off white solid; ^{1}H NMR (400 MHz, CD_3OD) δ 9.09 (s, 1H), 8.81 (s, 2H), 8.00 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 13.2 Hz, 1H), 6.23 (br s, 1H), 3.65 (s, 2H), 3.03 (m, 2H), 2.76 (m, 1H), 2.27 (s, 3H), 2.25 (s, 3H), 2.25 (m, 2H), 1.80-1.68 (m, 4H); ESMS *m/z* 508.2 ($M+H^+$).

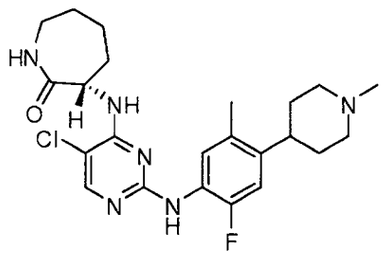
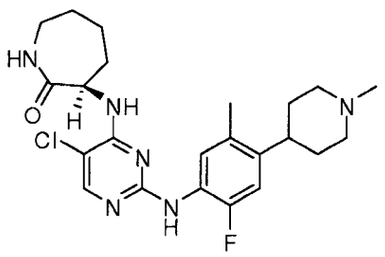
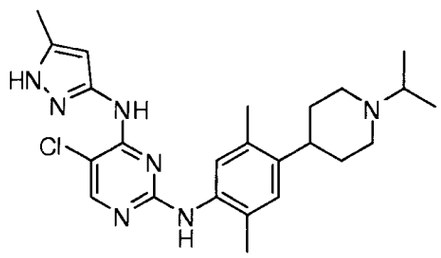
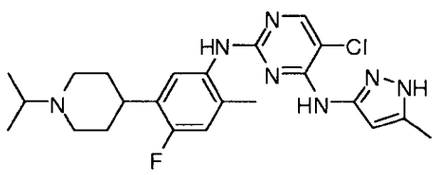
[0206] The following compounds in Table 1 are obtained by repeating the procedures described in examples above and using appropriate starting materials.

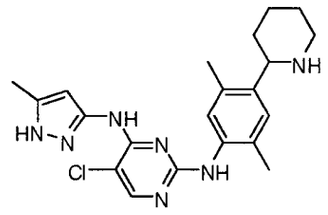
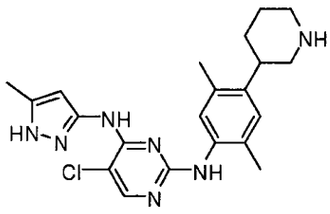
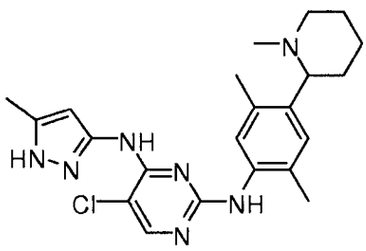
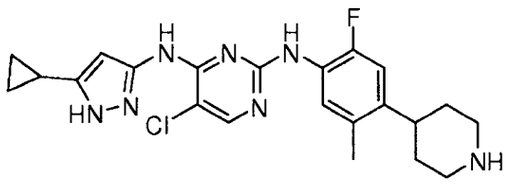
Table 1

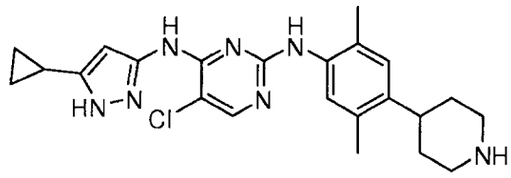
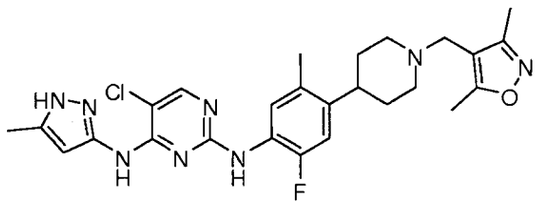
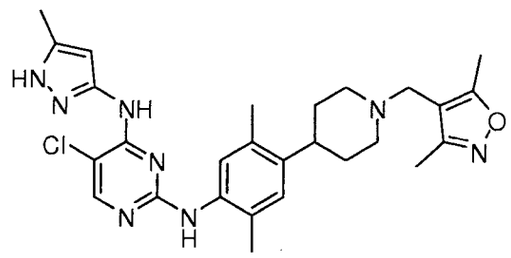
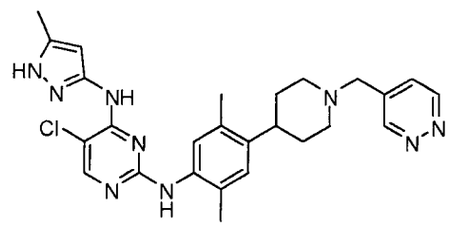
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
1	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	^{1}H NMR (400 MHz, DMSO-d6) δ 10.33 (br, 1H), 9.90 (br, 1H0, 9.60 (br, 1H), 8.22 (s, 1H), 7.56 (d, 1H), 7.00 (d, 1H), 6.20 (s, 1H), 3.53-3.50 (m, 2H), 3.16-3.10 (m, 2H), 2.97-2.92 (m,1H), 2.81 (d, 3H), 2.26 (s, 3H), 2.16 (s, 3H), 1.94-1.91 (m, 2H), 1.83-1.73 (m, 2H); ESMS *m/z* 430.1 ($M + H^+$).	0.011

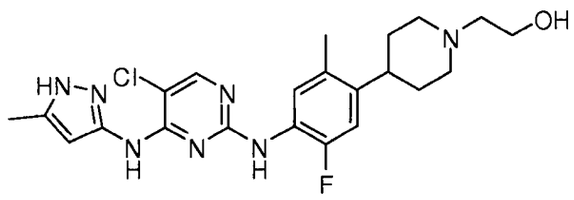
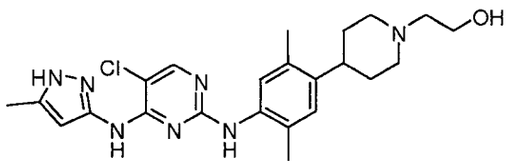
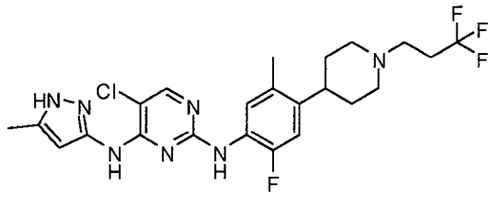
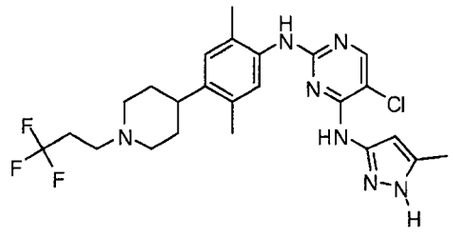
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
2	 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 416.1 (M + H^+).	0.050
3	 5-chloro-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 470.2 (M + H^+).	0.104
4	 N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine	ESMS *m/z* 450.2 (M + H^+).	0.150
5	 N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-5-methyl-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 450.3 (M + H^+).	0.805

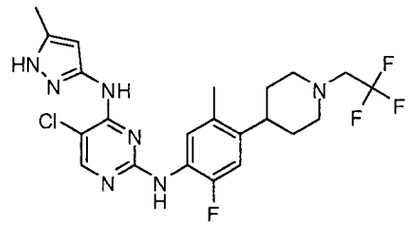
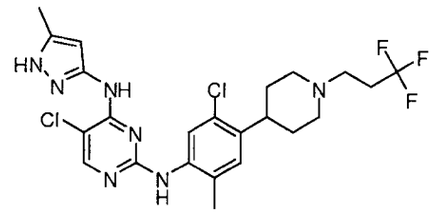
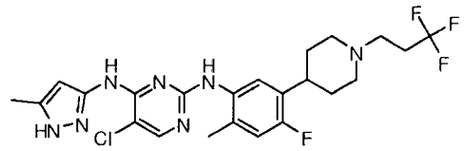
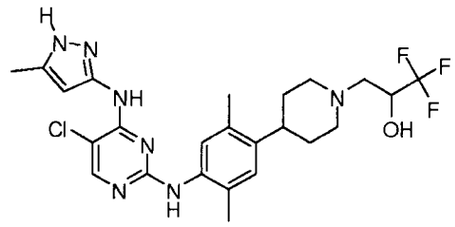
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
6	 5-chloro-N2-(2,5-dimethyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 426.2 (M + H^+).	0.015
7	 5-chloro-N2-(5-chloro-2-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 446.1 (M + H^+).	0.015
8	 5-chloro-N2-(4-fluoro-2-methyl-5-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 461.2 (M + H^+).	1.93
9	 3-(5-chloro-2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)azepan-2-one	ESMS *m/z* 461.2 (M + H^+).	0.087

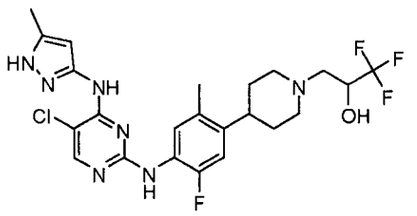
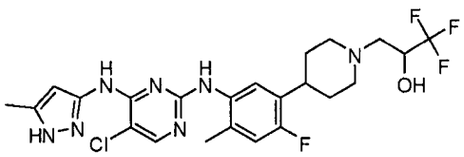
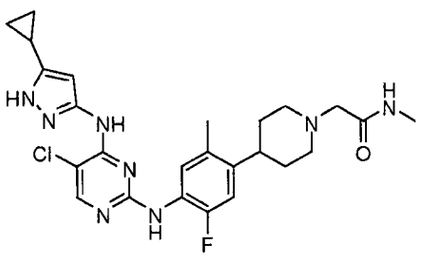
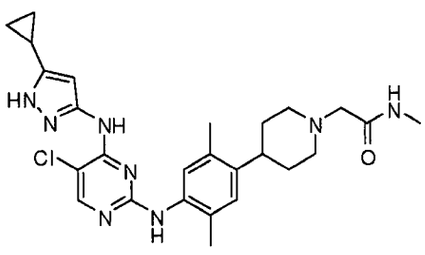
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
10	 (S)-3-(5-chloro-2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)azepan-2-one	ESMS *m/z* 461.2 (M + H^+).	0.869
11	 (R)-3-(5-chloro-2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)azepan-2-one	ESMS *m/z* 461.2 (M + H^+).	0.065
12	 5-chloro-N2-(4-(1-isopropylpiperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 454.2 (M + H^+).	0.010
13	 5-chloro-N2-(4-fluoro-5-(1-isopropylpiperidin-4-yl)-2-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 458.2 (M + H^+).	

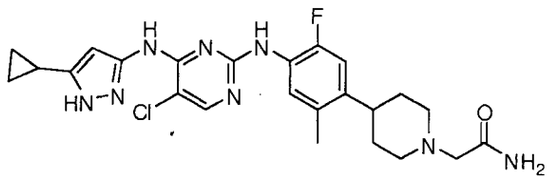
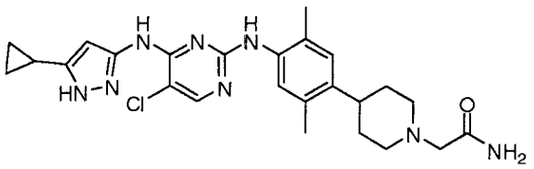
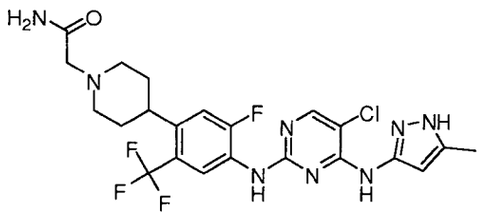
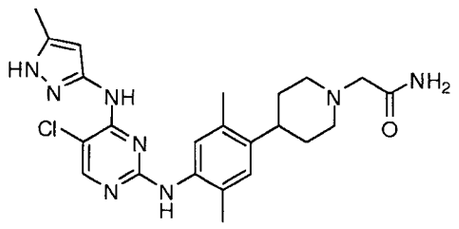
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
14	 5-chloro-N2-(2,5-dimethyl-4-(piperidin-2-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS m/z 412.2 (M + H+).	0.016
15	 5-chloro-N2-(2,5-dimethyl-4-(piperidin-3-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 412.2 (M + H^+).	0.050
16	 5-chloro-N2-(2,5-dimethyl-4-(1-methylpiperidin-2-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 426.2 (M + H^+).	0.019
17	 5-chloro-N4-(5-cyclopropyl-1H-pyrazol-3-yl)-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)pyrimidine-2,4-diamine	ESMS *m/z* 442.2 (M + H^+).	0.160

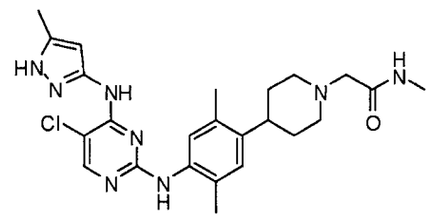
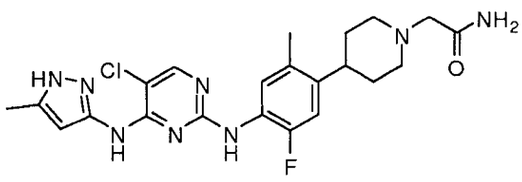
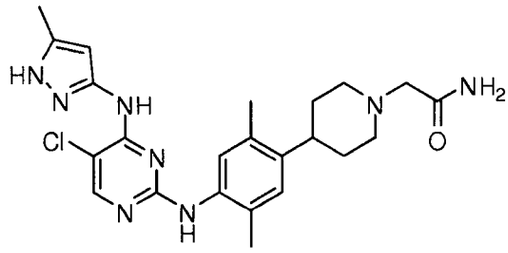
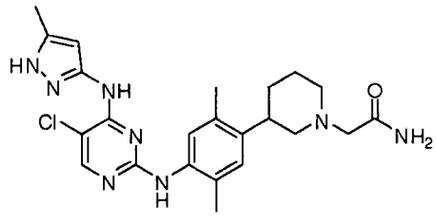
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
18	 5-chloro-N4-(5-cyclopropyl-1H-pyrazol-3-yl)-N2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)pyrimidine-2,4-diamine	ESMS *m/z* 438.2 (M + H^+).	0.095
19	 5-Chloro-N2-(4-(1-((3,5-dimethylisoxazol-4-yl)methyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	1H NMR (400 MHz, MeOD-d4) 8.12 (s, 1H), 7.75 (d, 1H), 7.03 (s, 1H), 6.27 (s, 1H), 4.25 (s, 2H), 3.69-3.67 (m, 2H), 3.27-3.20 (m, 3H), 2.54 (s, 3H), 2.37 (s, 3H), 2.34 (s, 3H), 2.30 (s, 3H), 2.10-1.95 (m, 4H);ESMS m/z 525.1 (M + H+).	0.056
20	 5-chloro-N2-(4-(1-((3,5-dimethylisoxazol-4-yl)methyl)piperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 521.2 (M + H^+).	0.011
21	 5-chloro-N2-(2,5-dimethyl-4-(1-(pyridazin-4-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 504.2 (M + H^+)	0.002

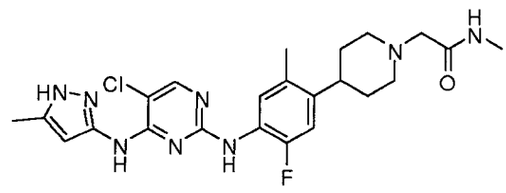
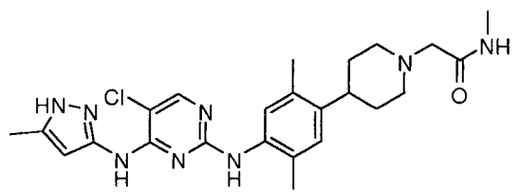
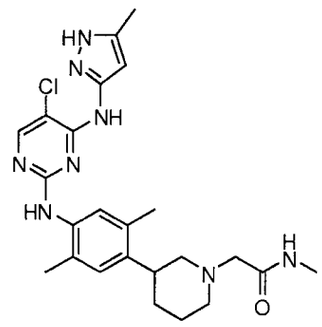
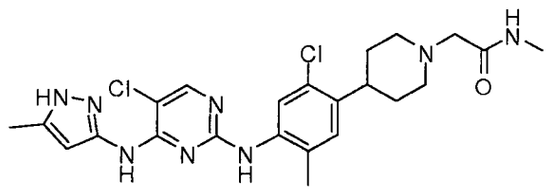
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
22	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)ethanol	ESMS m/z 460.2 (M + H+).	0.059
23	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)ethanol	ESMS *m/z* 456.21 (M + H^+).	0.006
24	 5-chloro-N^2-(2-fluoro-5-methyl-4-(1-(3,3,3-trifluoropropyl)piperidin-4-yl)phenyl)- N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 512.2 (M + H^+).	0.085
25	 5-chloro-N2-(2,5-dimethyl-4-(1-(3,3,3-trifluoropropyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 508.2 (M + H^+).	0.031

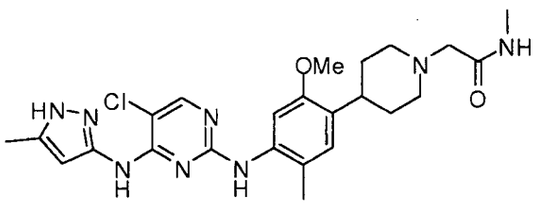
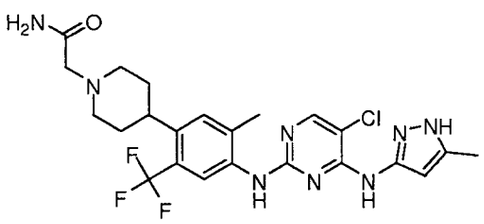
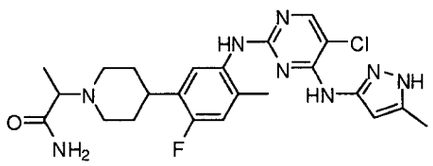
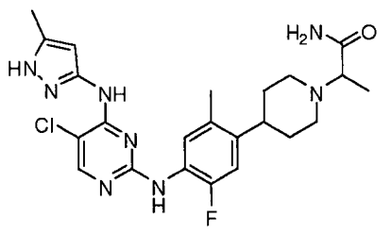
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
26	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 498.2 (M + H^+).	0.142
27	 5-chloro-N2-(5-chloro-2-methyl-4-(1-(3,3,3-trifluoropropyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 528.2 (M + H^+).	0.044
28	 5-chloro-N2-(4-fluoro-2-methyl-5-(1-(3,3,3-trifluoropropyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 512.2 (M + H^+).	5.46
29	 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl) piperidin-1-yl)-1,1,1-trifluoropropan-2-ol	ESMS *m/z* 524.2 (M + H^+).	0.023

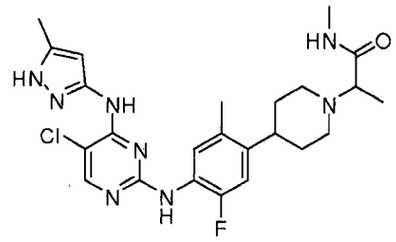
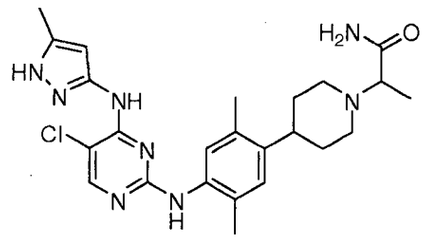
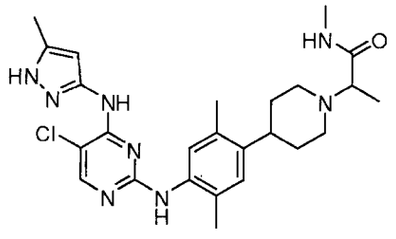
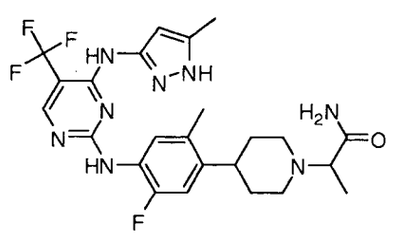
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
30	 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino) pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl) piperidin-1-yl)-1,1,1-trifluoropropan-2-ol	ESMS *m/z* 528.2 (M + H^+).	0.071
31	 3-(4-(5-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2-fluoro-4-methylphenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol	ESMS m/z 528.2 (M + H+).	6.47
32	 2-(4-(4-(5-chloro-4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-N-methylacetamide	ESMS *m/z* 513.2 (M + H^+).	0.042
33	 2-(4-(4-(5-chloro-4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide	ESMS *m/z* 509.2 (M + H^+).	0.006

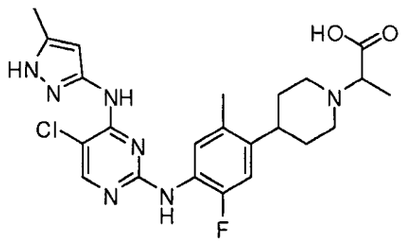
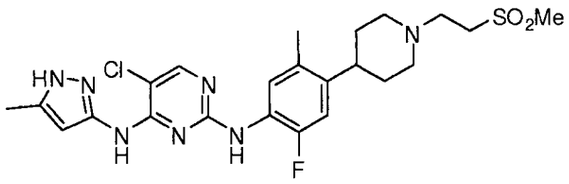
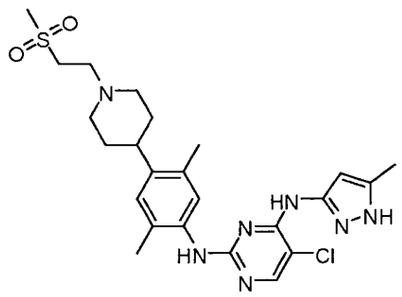
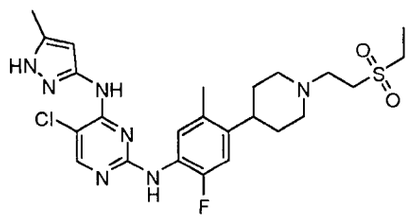
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
34	 2-(4-(4-(5-chloro-4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)acetamide	ESMS *m/z* 499.2 (M + H^+).	0.049
35	 2-(4-(4-(5-chloro-4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)acetamide	ESMS *m/z* 495.2 (M + H^+).	0.011
36	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-(trifluoromethyl)phenyl)piperidin-1-yl)acetamide	ESMS *m/z* 527.2 (M + H^+).	0.019
37	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)acetamide	ESMS *m/z* 469.2 (M + H^+).	0.013

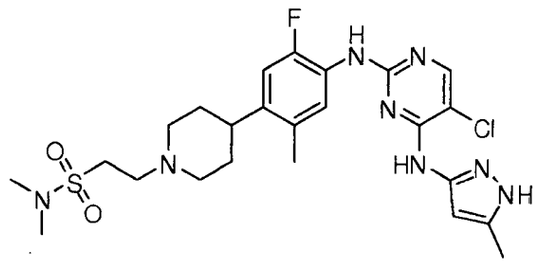
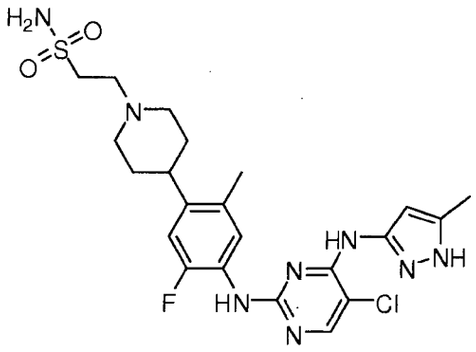
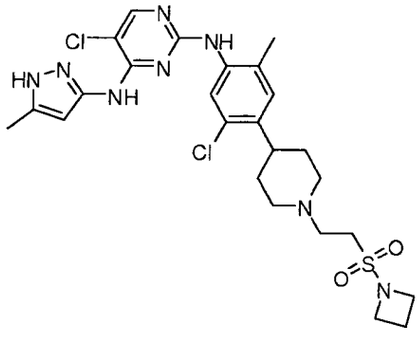
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
38	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide	ESMS *m/z* 483.2 (M + H^+).	0.010
39	 2-(4-(4-(5-Chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)acetamide	^{1}H NMR (400 MHz, MeOD-d_4) δ 8.11 (s, 1H), 7.76 (d 1H), 7.09 (d, 1H), 6.27 (s, 1H), 4.0 (s, 2H), 3.75-3.73 (m, 2H), 3.22-3.13 (m, 3H), 2.34 (s, 3H), 2.30 (s, 3H), 2.04 - 2.00 (m, 4H); ESMS *m/z* 473.2 (M + H^+).	0.019
40	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)acetamide	ESMS *m/z* 469.2 (M + H^+).	
41	 2-(3-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)acetamide	ESMS *m/z* 469.2 (M + H^+).	0.026

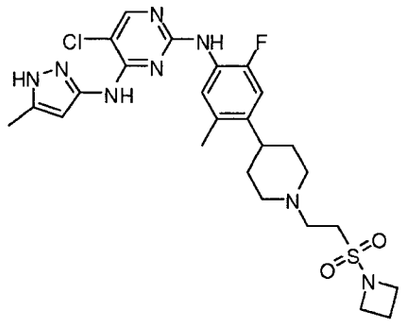
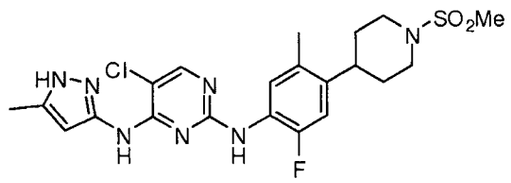
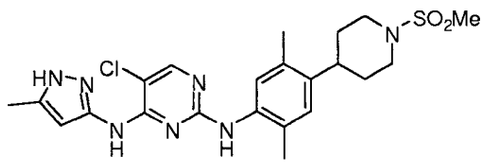
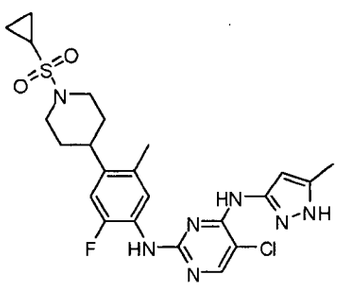
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
42	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-N-methylacetamide	ESMS *m/z* 487.2 (M + H^+).	0.019
43	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide	ESMS *m/z* 483.2 (M + H^+).	
44	 2-(3-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide	ESMS *m/z* 483.2 (M + H^+).	0.015
45	 2-(4-(2-chloro-4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-methylphenyl)piperidin-1-yl)-N-methylacetamide	ESMS *m/z* 503.2 (M + H^+).	0.018

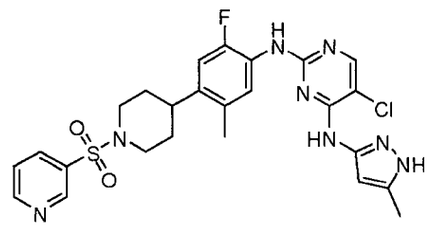
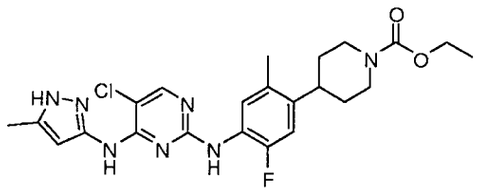
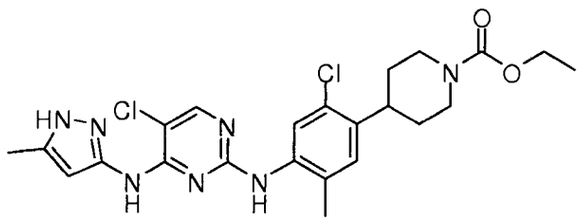
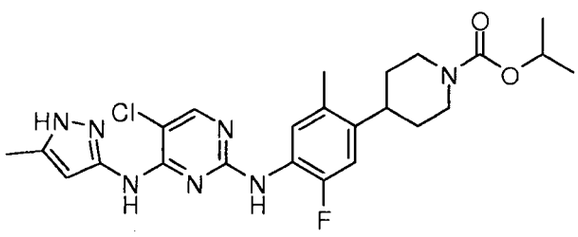
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
46	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2-methoxy-5-methylphenyl)piperidin-1-yl)-N-methylacetamide	ESMS *m/z* 499.2 (M + H^+).	0.013
47	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-methyl-2-(trifluoromethyl)phenyl)piperidin-1-yl)acetamide	ESMS *m/z* 523.2 (M + H^+).	0.022
48	 2-(4-(5-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2-fluoro-4-methylphenyl)piperidin-1-yl)propanamide	ESMS *m/z* 487.2 (M + H^+).	3.68
49	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)propanamide	ESMS *m/z* 487.2 (M + H^+).	0.015

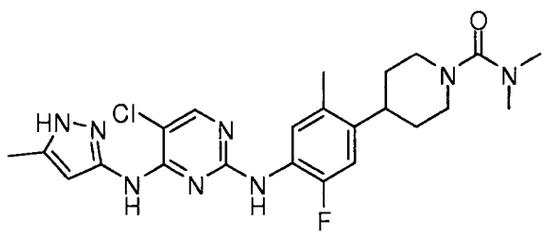
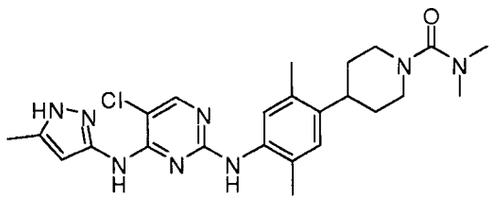
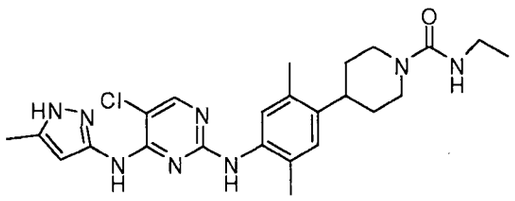
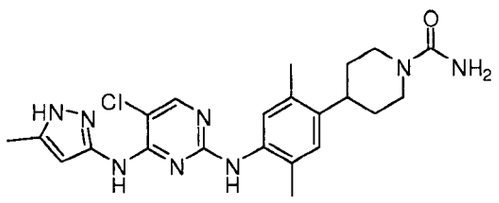
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
50	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-N-methylpropanamide	ESMS m/z 501.2 (M + H+).	0.022
51	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)propanamide	ESMS *m/z* 483.2 (M + H^+).	0.009
52	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylpropanamide	ESMS *m/z* 497.2 (M + H^+).	0.006
53	 2-(4-(5-fluoro-2-methyl-4-(4-(5-methyl-1H-pyrazol-3-ylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)piperidin-1-yl)propanamide	ESMS *m/z* 521.2 (M + H^+).	0.078

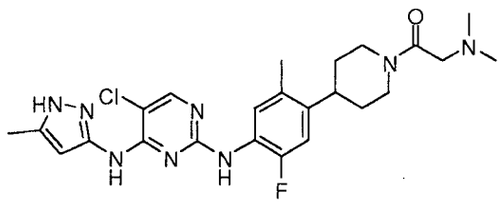
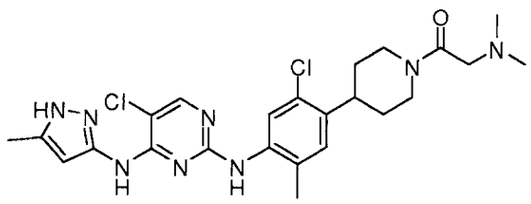
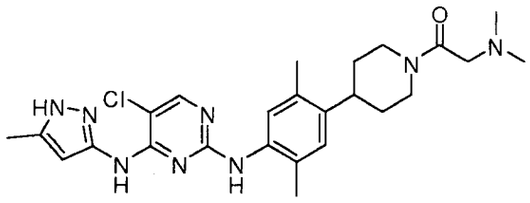
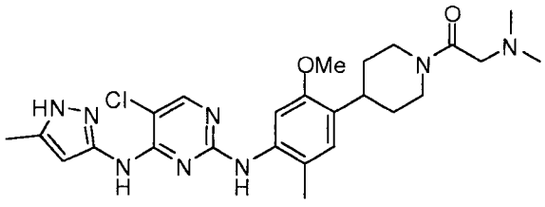
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
54	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)propanoic acid	ESMS *m/z* 488.2 (M + H^+).	1.53
55	 5-Chloro-N2-(2-fluoro-5-methyl-4-(1-(2-(methylsulfonyl)ethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS m/z 522.1 (M + H+).	0.024
56	 5-chloro-N2-(2,5-dimethyl-4-(1-(2-(methylsulfonyl)ethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 518.2 (M + H^+).	0.006
57	 5-chloro-N2-(4-(1-(2-(ethylsulfonyl)ethyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 536.2 (M + H^+).	0.021

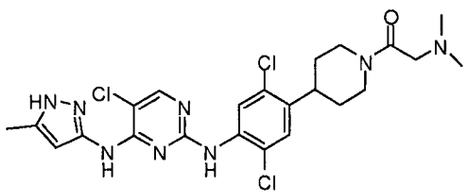
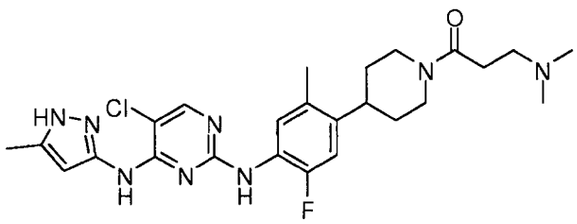
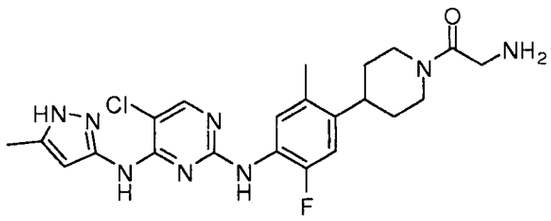
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
58	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-N,N-dimethylethanesulfonamide	ESMS *m/z* 551.2 (M + H^+).	0.036
59	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)ethanesulfonamide	ESMS *m/z* 523.2 (M + H^+).	0.038
60	 N2-(4-(1-(2-(azetidin-1-ylsulfonyl)ethyl)piperidin-4-yl)-5-chloro-2-methylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 579.2 (M + H^+).	0.011

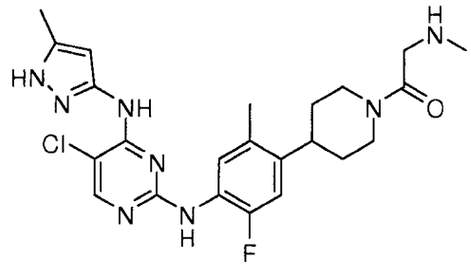
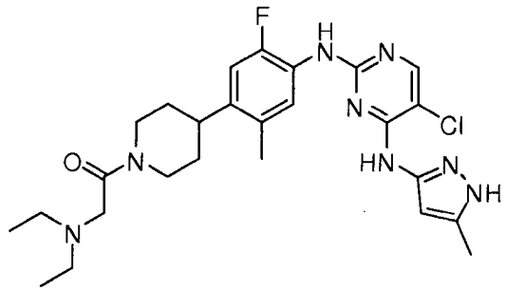
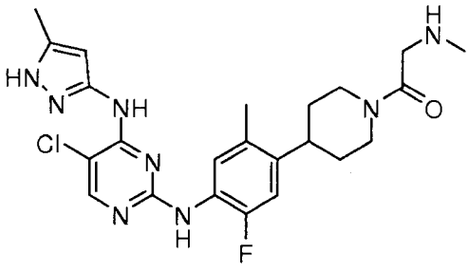
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
61	 N2-(4-(1-(2-(azetidin-1-ylsulfonyl)ethyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 563.2 (M + H^+).	0.056
62	 5-Chloro-N2-(2-fluoro-5-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 494.2 (M + H^+).	0.005
63	 5-chloro-N2-(2,5-dimethyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 490.2 (M + H^+).	0.002
64	 5-chloro-N2-(4-(1-(cyclopropylsulfonyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 520.2 (M + H^+).	0.059

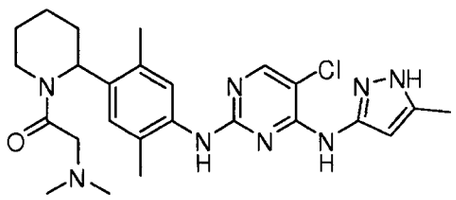
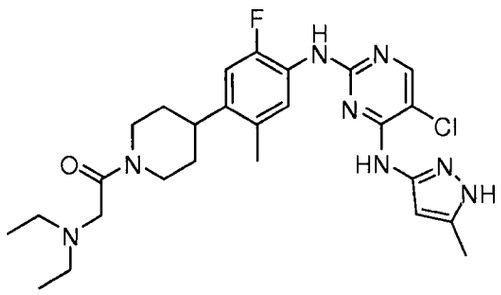
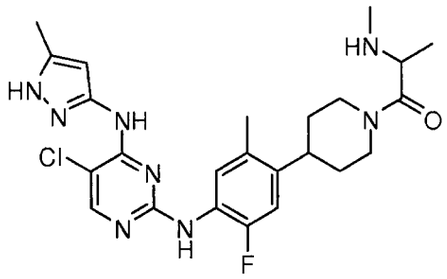
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
65	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(pyridin-3-ylsulfonyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 557.2 (M + H^+).	0.076
66	 Ethyl 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidine-1-carboxylate	^{1}H NMR (400 MHz, MeOD-d_4) δ 8.13 (s, 1H), 7.54 (d, 1H), 7.10 (d, 1H), 6.28 (s, 1H), 4.30-4.26 (m, 2H), 4.14 (q, 2H), 2.99-2.96 (m, 3H), 2.33 (s, 3H), 2.29 (s, 3H), 1.8-1.77 (m, 2H), 1.64-1.55 (m, 2H), 1.28 (t, 3H); ESMS *m/z* 488.2 (M + H^+).	0.064
67	 ethyl 4-(2-chloro-4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-methylphenyl)piperidine-1-carboxylate	ESMS *m/z* 504.2 (M + H^+).	0.182
68	 isopropyl 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidine-1-carboxylate	ESMS *m/z* 502.2 (M + H^+).	0.080

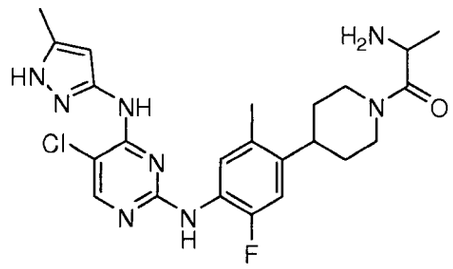
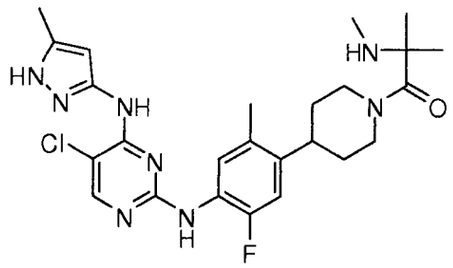
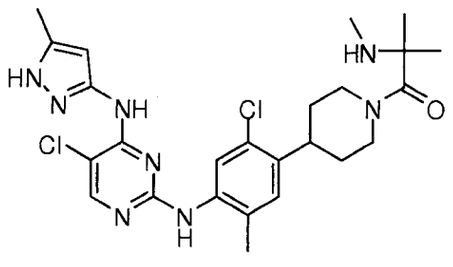
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
69	 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)-N,N-dimethylpiperidine-1-carboxamide	ESMS m/z 487.2 (M + H+).	0.011
70	 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)-N,N-dimethylpiperidine-1-carboxamide	ESMS *m/z* 483.2 (M + H^+).	0.006
71	 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)-N-ethylpiperidine-1-carboxamide	ESMS *m/z* 483.2 (M + H^+).	0.002
72	 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidine-1-carboxamide	ESMS *m/z* 455.2 (M + H^+).	0.006

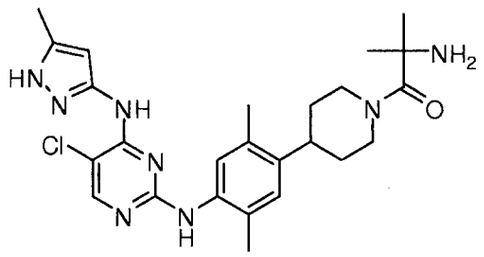
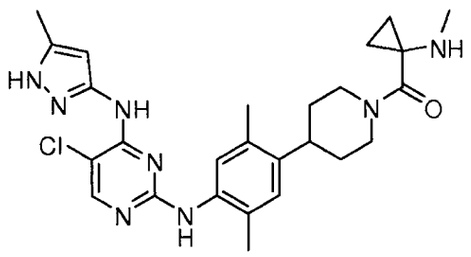
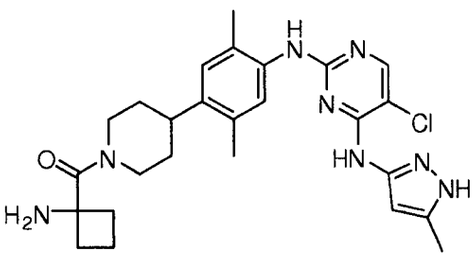
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
73	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone	^{1}H NMR (400 MHz, MeOD-d_4) δ 8.08 (s, 1H), 7.71 (d, 1H), 7.03 (d, 1H), 6.26 (s, 1H), 4.71-4.67 (m, 2H), 3.81-3.77 (m, 2H), 3.14-3.12 (m, 2H), 2.98 (s, 3H), 2.96 (s, 3H), 2.90-2.83 (m, 1H), 2.34 (s, 3H), 2.28 (s, 3H), 1.87 (d, 2H), 1.76-1.55 (m, 2H); ESMS *m/z* 501.2 (M + H$^+$).	0.019
74	 1-(4-(2-chloro-4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-methylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone	ESMS *m/z* 517.2 (M + H$^+$).	0.007
75	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone	ESMS *m/z* 497.2 (M + H$^+$).	0.011
76	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2-methoxy-5-methylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone	ESMS *m/z* 513.2 (M + H$^+$).	0.009

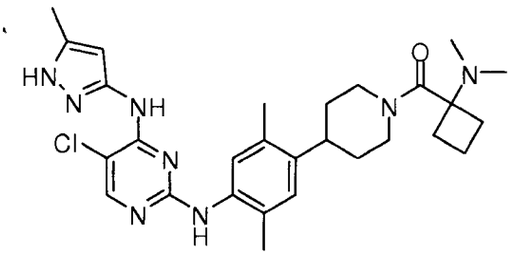
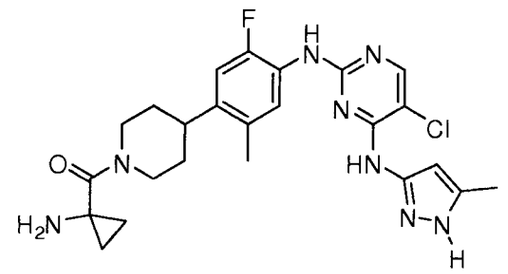
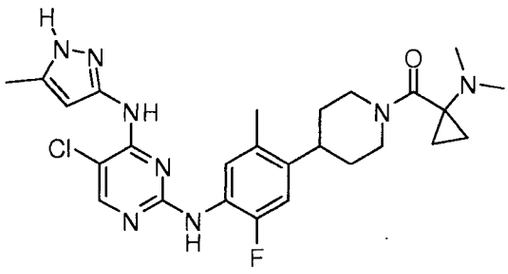
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
77	 1-(4-(2,5-dichloro-4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)phenyl)piperidin-1-yl)-2-(dimethylamino)ethanone	ESMS *m/z* 537.1 (M + H^+).	0.007
78	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-3-(dimethylamino)propan-1-one	ESMS *m/z* 515.2 (M + H^+).	0.138
79	 2-amino-1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)ethanone	ESMS *m/z* 473.2 (M + H^+).	0.075

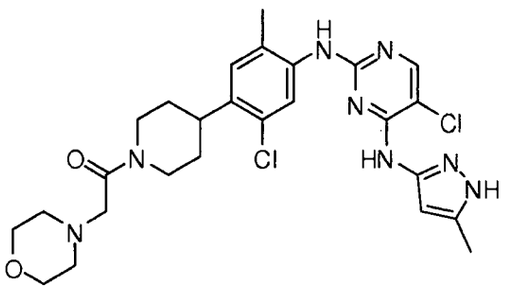
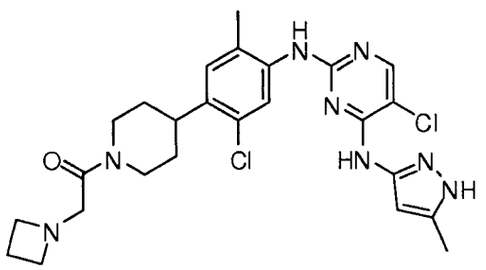
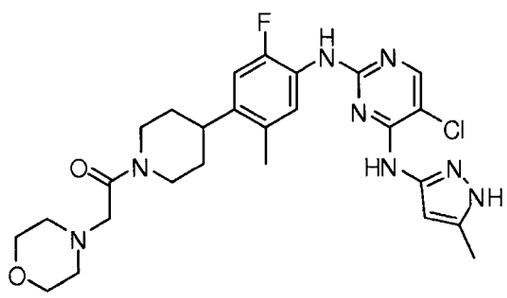
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
80	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(methylamino)ethanone	ESMS *m/z* 487.2 (M + H^+).	0.103
81	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(diethylamino)ethanone	ESMS *m/z* 529.3 (M + H^+).	0.030
82	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(methylamino)ethanone	ESMS *m/z* 487.2 (M + H^+).	

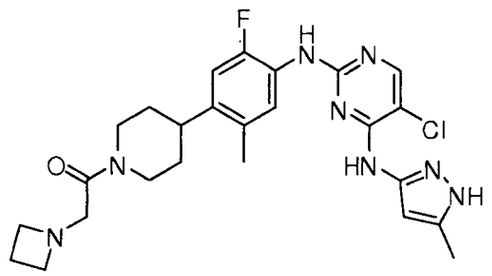
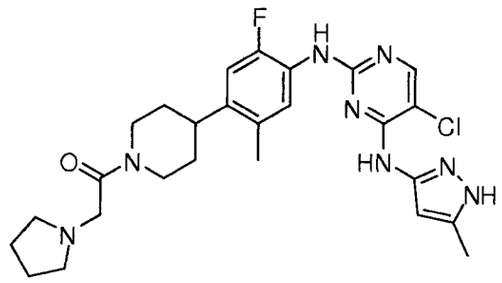
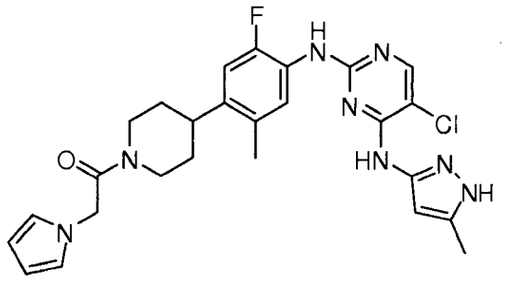
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
83	 1-(2-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone	ESMS *m/z* 497.2 (M + H^+).	0.013
84	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(diethylamino)ethanone	ESMS *m/z* 529.3 (M + H^+).	
85	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(methylamino)propan-1-one	ESMS *m/z* 501.2 (M + H^+).	0.042

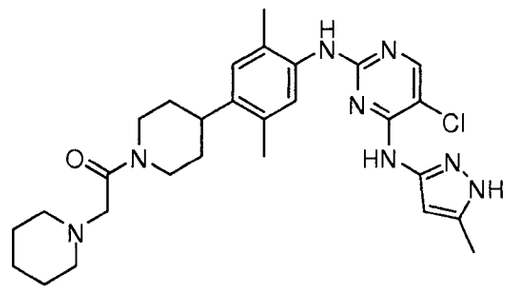
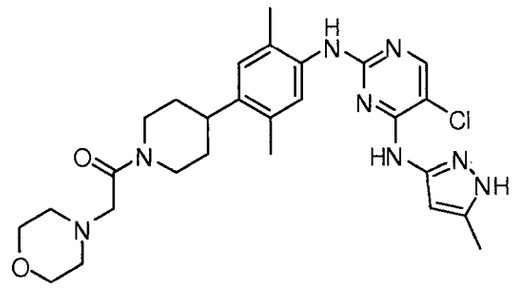
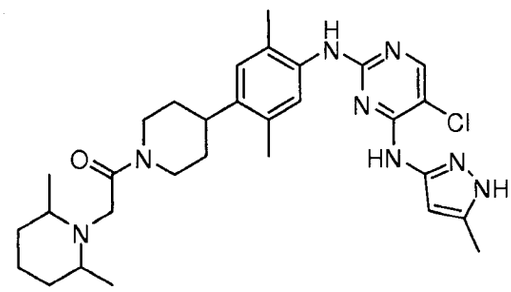
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
86	 2-amino-1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)propan-1-one	ESMS *m/z* 487.2 (M + H^+).	0.141
87	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-methyl-2-(methylamino)propan-1-one	ESMS *m/z* 515.2 (M + H^+).	0.017
88	 1-(4-(2-chloro-4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-methylphenyl)piperidin-1-yl)-2-methyl-2-(methylamino)propan-1-one	ESMS *m/z* 531.2 (M + H^+).	0.007

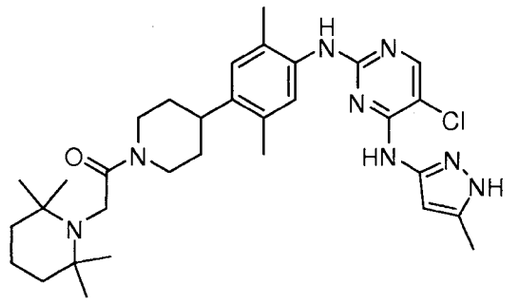
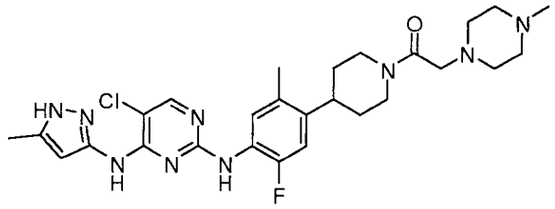
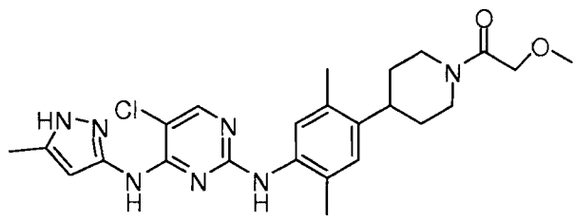
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
89	 2-amino-1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-methylpropan-1-one	ESMS *m/z* 497.2 (M + H^+).	0.023
90	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)(1-(methylamino)cyclopropyl)methanone	ESMS *m/z* 509.2 (M + H^+).	0.005
91	 (1-aminocyclobutyl)(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)methanone	ESMS *m/z* 509.2 (M + H^+).	0.052

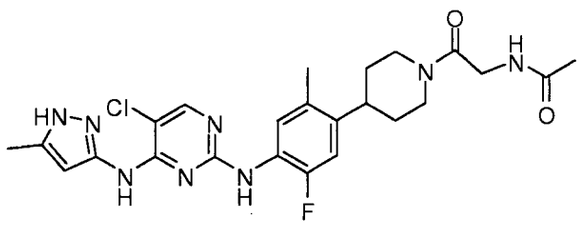
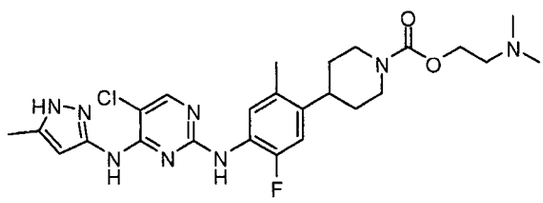
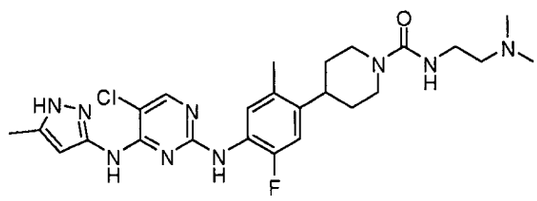
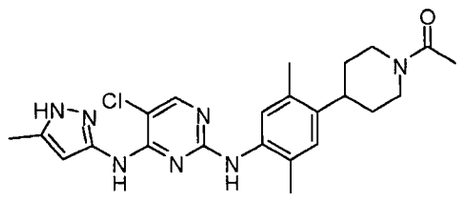
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
92	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)(1-(dimethylamino)cyclobutyl)methanone	ESMS *m/z* 537.3 (M + H^+).	0.015
93	 (1-aminocyclopropyl)(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)methanone	ESMS *m/z* 499.2 (M + H^+).	0.033
94	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-(dimethylamino)cyclopropyl)methanone	ESMS *m/z* 527.2 (M + H^+).	0.013

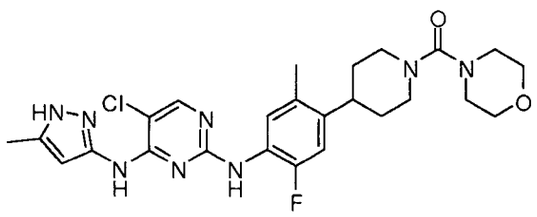
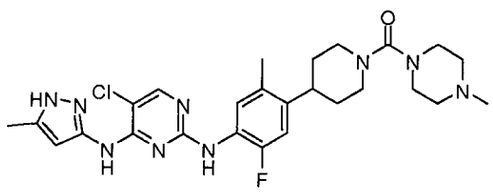
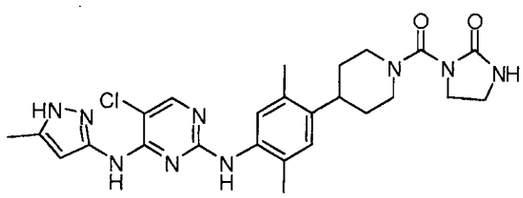
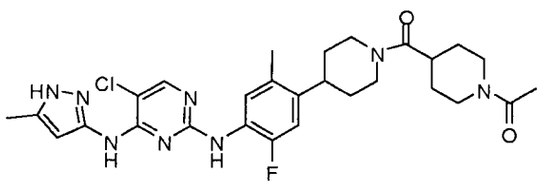
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
95	 1-(4-(2-chloro-4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-methylphenyl)piperidin-1-yl)-2-morpholinoethanone	ESMS *m/z* 559.2 (M + H^+).	0.006
96	 2-(azetidin-1-yl)-1-(4-(2-chloro-4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-methylphenyl)piperidin-1-yl)ethanone	ESMS *m/z* 529.2 (M + H^+).	0.024
97	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-morpholinoethanone	ESMS *m/z* 543.2 (M + H^+).	0.020

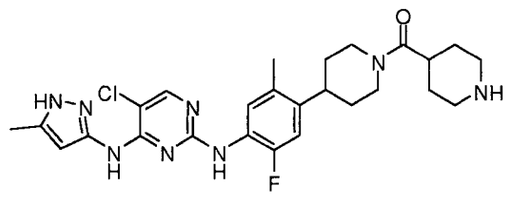
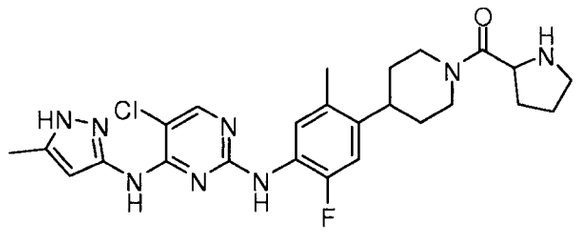
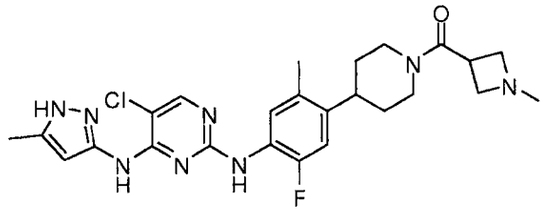
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
98	 2-(azetidin-1-yl)-1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)ethanone	ESMS *m/z* 513.2 (M + H^+).	0.064
99	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(pyrrolidin-1-yl)ethanone	ESMS *m/z* 527.2 (M + H^+).	0.038
100	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(1H-pyrrol-1-yl)ethanone	ESMS *m/z* 523.2 (M + H^+).	0.025

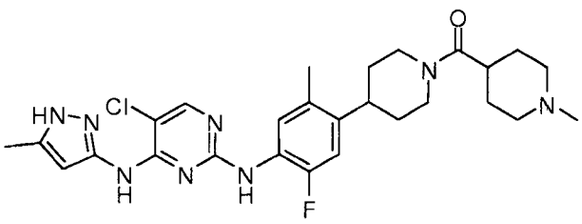
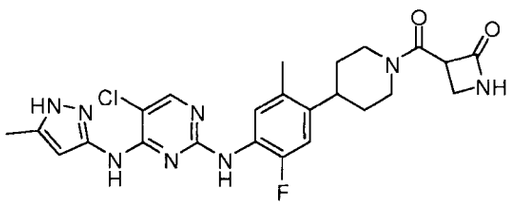
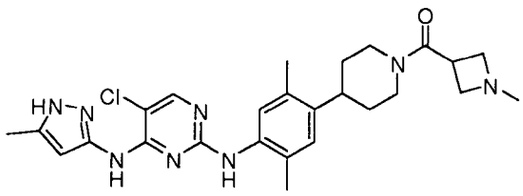
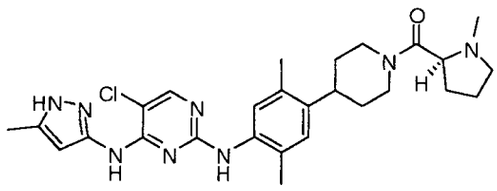
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
101	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(piperidin-1-yl)ethanone	ESMS *m/z* 537.3 (M + H^+).	0.007
102	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-morpholinoethanone	ESMS *m/z* 539.3 (M + H^+).	0.009
103	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(2,6-dimethylpiperidin-1-yl)ethanone	ESMS *m/z* 565.3 (M + H^+).	0.009

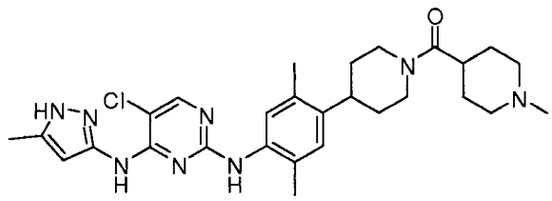
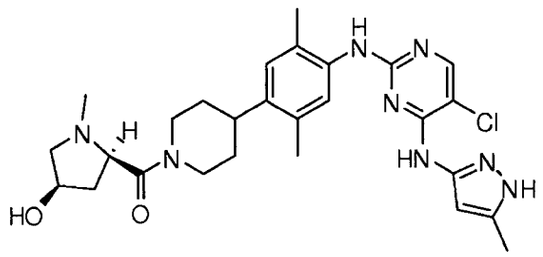
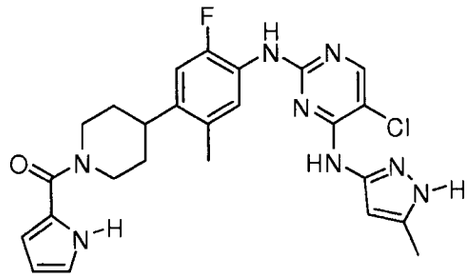
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
104	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(2,2,6,6-tetramethylpiperidin-1-yl)ethanone	ESMS *m/z* 593.3 (M + H^+).	0.018
105	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(4-methylpiperazin-1-yl)ethanone	ESMS m/z 556.3 (M + H^+).	0.051
106	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-methoxyethanone	ESMS *m/z* 484.2 (M + H^+).	0.002

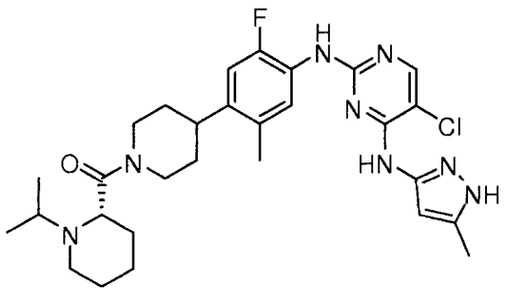
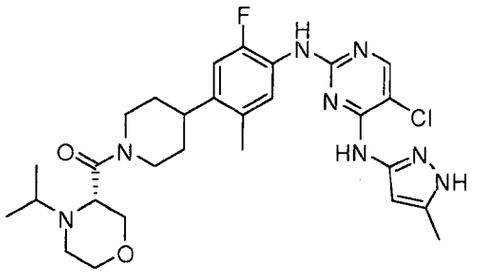
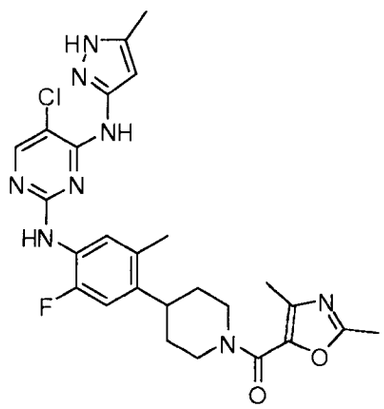
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
107	 N-(2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-oxoethyl)acetamide	ESMS *m/z* 515.2 (M + H^+).	0.057
108	 2-(dimethylamino)ethyl 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidine-1-carboxylate	ESMS *m/z* 531.2 (M + H^+).	0.053
109	 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)-N-(2-(dimethylamino)ethyl)piperidine-1-carboxamide	ESMS *m/z* 530.2 (M + H^+).	0.060
110	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)ethanone	ESMS *m/z* 454.2 (M + H^+).	0.013

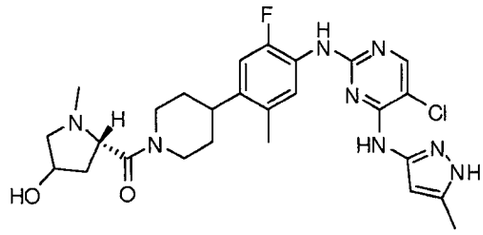
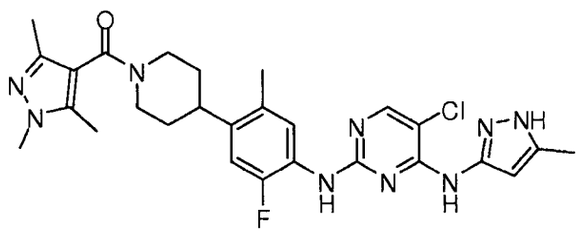
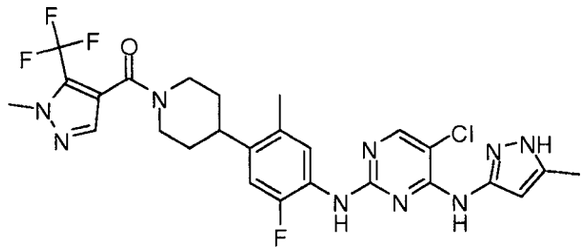
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
111	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(morpholino)methanone	ESMS *m/z* 529.2 (M + H^+).	0.008
112	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(4-methylpiperazin-1-yl)methanone	ESMS *m/z* 542.2 (M + H^+).	0.021
113	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidine-1-carbonyl)imidazolidin-2-one	ESMS *m/z* 524.2 (M + H^+).	0.013
114	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-methoxyethanone	ESMS *m/z* 569.2 (M + H^+).	0.048

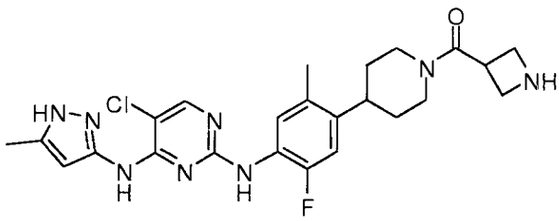
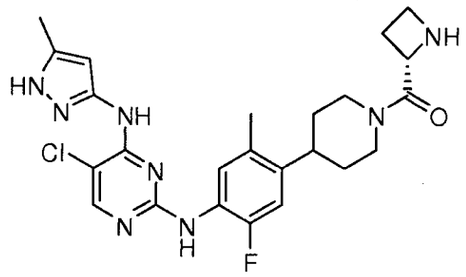
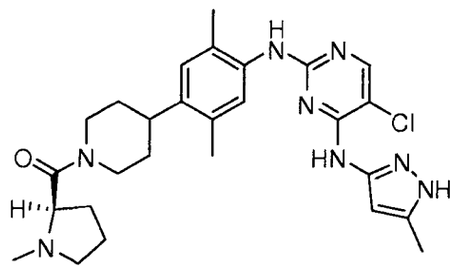
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
115	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(piperidin-4-yl)methanone	ESMS *m/z* 527.2 (M + H^+).	1.57
116	 (S)-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(pyrrolidin-2-yl)methanone	ESMS *m/z* 513.2 (M + H^+).	0.137
117	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-methylazetidin-3-yl)methanone	ESMS *m/z* 513.2(M + H^+).	0.099

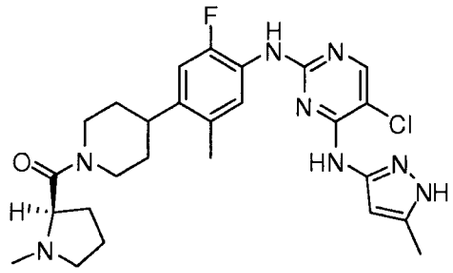
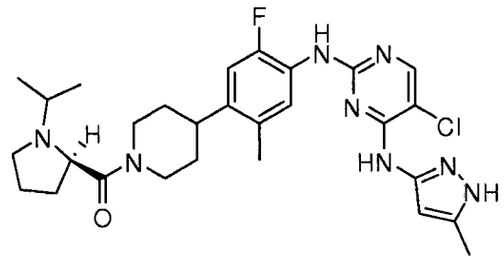
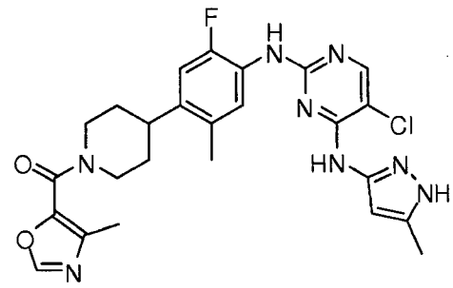
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
118	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-methylpiperidin-4-yl)methanone	ESMS *m/z* 541.2 (M + H^+).	0.081
119	 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidine-1-carbonyl)azetidin-2-one	ESMS *m/z* 513.2 (M + H^+).	2.99
120	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)(1-methylazetidin-3-yl)methanone	ESMS *m/z* 509.2 (M + H^+).	0.025
121	 (*S*)-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)(1-methylpyrrolidin-2-yl)methanone	ESMS *m/z* 523.2 (M + H^+).	0.017

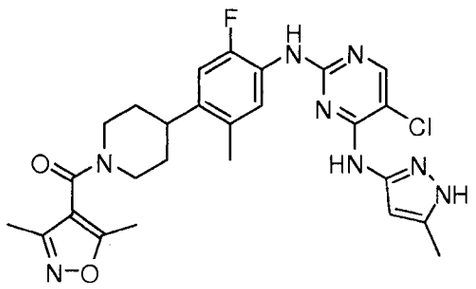
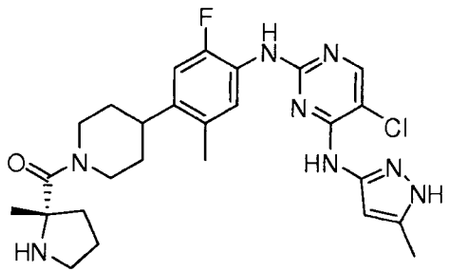
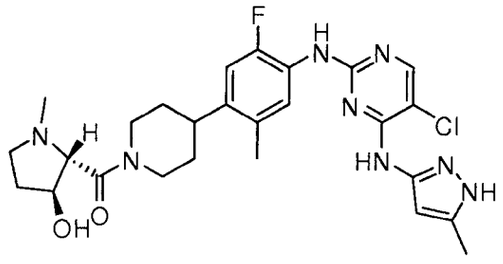
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
122	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)(1-methylpiperidin-4-yl)methanone	ESMS *m/z* 537.2 (M + H^+).	
123	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)((2R,4R)-4-hydroxy-1-methylpyrrolidin-2-yl)methanone	ESMS *m/z* 539.3 (M + H^+).	0.048
124	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1H-pyrrol-2-yl)methanone	ESMS *m/z* 509.2 (M + H^+).	0.145

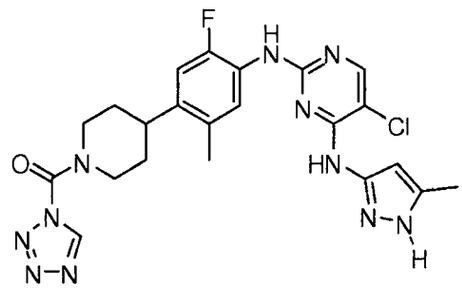
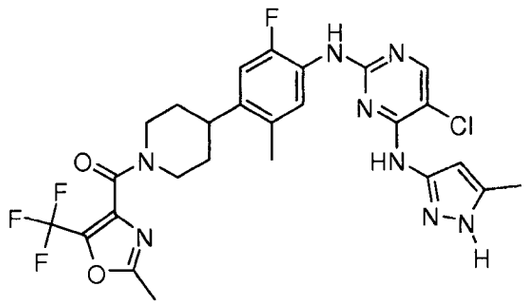
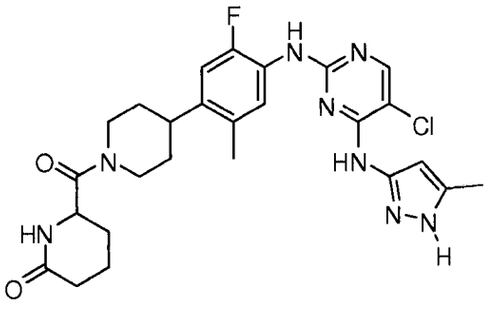
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
125	 (S)-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-isopropylpiperidin-2-yl)methanone	ESMS *m/z* 569.3 (M + H^+).	0.012
126	 (S)-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(4-isopropylmorpholin-3-yl)methanone	ESMS *m/z* 571.3 (M + H^+).	0.029
127	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(2,4-dimethyloxazol-5-yl)methanone	ESMS *m/z* 539.2 (M + H^+).	0.027

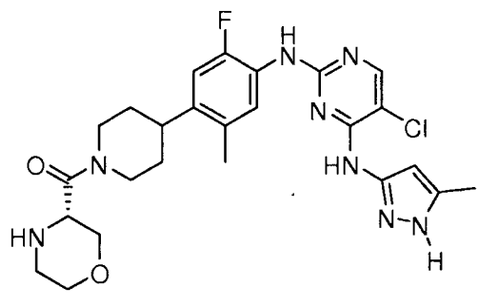
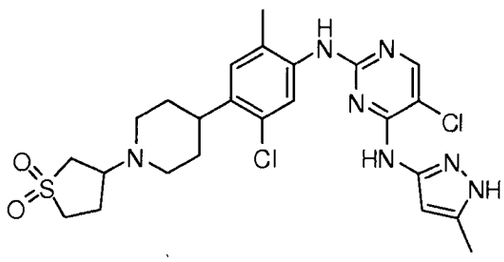
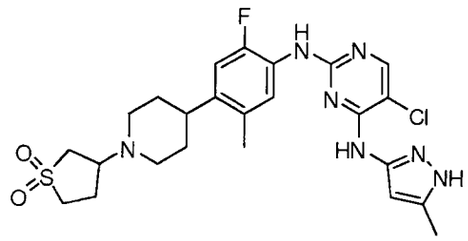
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
128	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)((2S)-4-hydroxy-1-methylpyrrolidin-2-yl)methanone	ESMS *m/z* 543.2 (M + H^+).	0.175
129	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1,3,5-trimethyl-1H-pyrazol-4-yl)methanone	ESMS *m/z* 552.2 (M + H^+).	0.025
130	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)methanone	ESMS *m/z* 592.2 (M + H^+).	0.061

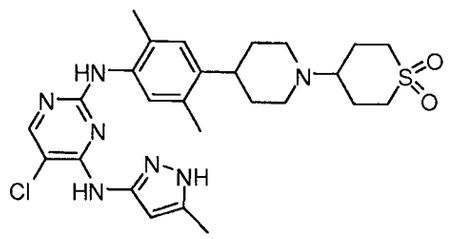
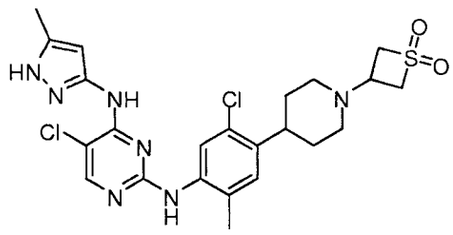
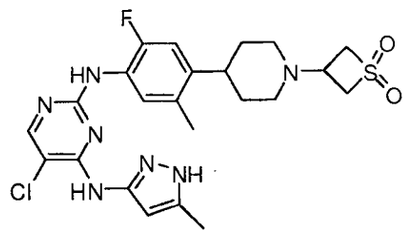
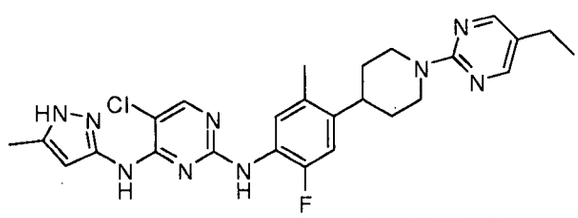
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
131	 azetidin-3-yl(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)methanone	^{1}H NMR (400 MHz, MeOD-d_4) δ 8.08 (s, 1H), 7.68 (d, 2H), 7.04 (d, 2H), 6.26 (s, 1H), 4.74-4.68 (m, 2H), 4.39-4.35 (m, 1H), 4.29-4.24 (m, 2H), 4.11 -4.07 (m, 1H), 3.74-3.71 (m, 1H), 3.25 -3.24 (m, 1H), 3.07-3.04 (m, 1H), 2.87-2.80 (m, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 1.87-1.84 (m, 2H), 1.66-1.56 (m, 2H); ESMS *m/z* 499.2 (M + H^+).	1.25
132	 (S)-azetidin-2-yl(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)methanone	ESMS m/z 499.2 (M + H+).	0.161
133	 (R)-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl) piperidin-1-yl)(1-methylpyrrolidin-2-yl)methanone	ESMS *m/z* 523.3 (M + H^+).	0.013

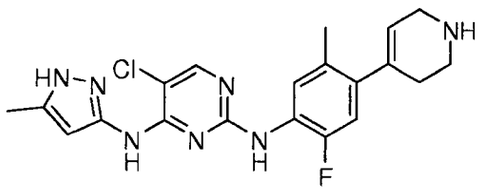
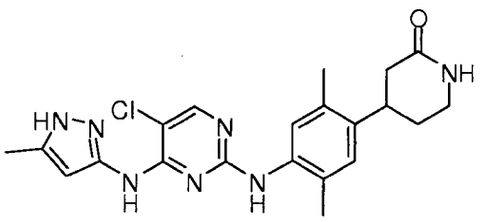
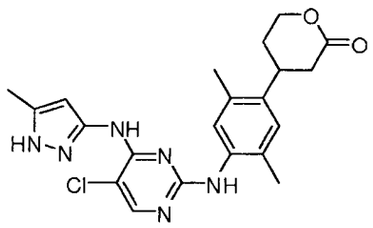
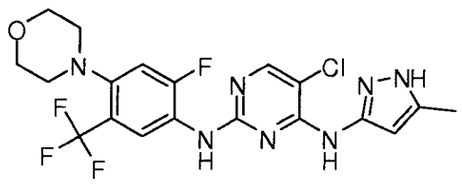
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
134	 (R)-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl) piperidin-1-yl)(1-methylpyrrolidin-2-yl)methanone	ESMS *m/z* 527.2 (M + H^+).	0.021
135	 (R)-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-isopropylpyrrolidin-2-yl)methanone	ESMS *m/z* 555.3 (M + H^+).	0.048
136	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(4-methyloxazol-5-yl)methanone	ESMS *m/z* 525.2 (M + H^+).	0.035

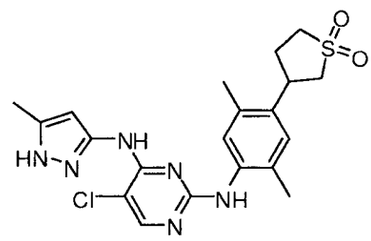
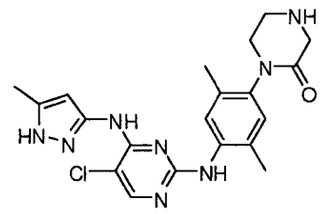
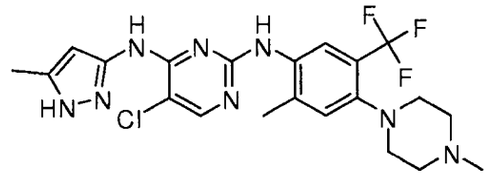
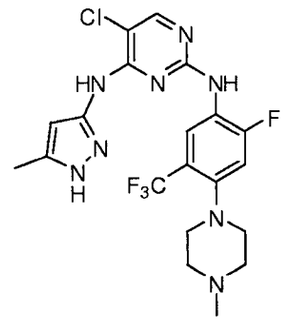
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
137	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(3,5-dimethylisoxazol-4-yl)methanone	ESMS *m/z* 539.2 (M + H^+).	0.018
138	 (S)-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(2-methylpyrrolidin-2-yl)methanone	ESMS *m/z* 527.2 (M + H^+).	0.091
139	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)((2S,3R)-3-hydroxy-1-methylpyrrolidin-2-yl)methanone	ESMS *m/z* 543.2 (M + H^+).	0.175

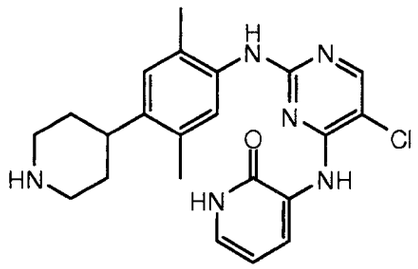
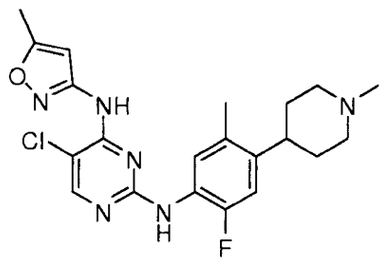
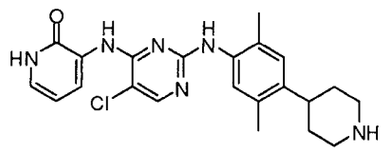
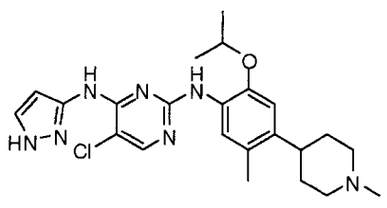
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
140	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1H-tetrazol-1-yl)methanone	ESMS *m/z* 512.2 (M + H^+).	0.139
141	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(2-methyl-5-(trifluoromethyl)oxazol-4-yl)methanone	ESMS *m/z* 593.2 (M + H^+).	0.069
142	 6-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidine-1-carbonyl)piperidin-2-one	ESMS *m/z* 541.2 (M + H^+).	0.282

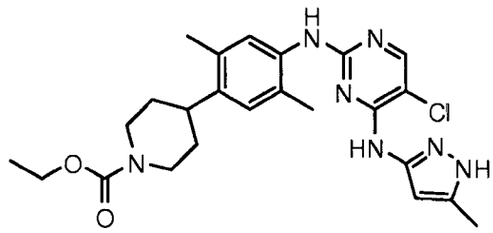
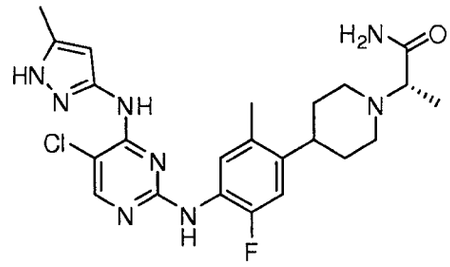
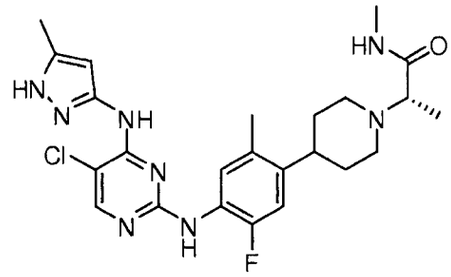
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
143	 (S)-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(morpholin-3-yl)methanone	ESMS *m/z* 529.2 (M + H^+).	0.071
144	 5-chloro-N^2-(2-methyl-5-chloro-4-(1-(tetrahydro-1,1-dioxido-3-thienyl)piperidin-4-yl)phenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 550.1 (M + H^+).	0.007
145	 5-chloro-N^2-(2-fluoro-5-methyl-4-(1-(tetrahydro-1,1-dioxido-3-thienyl)piperidin-4-yl)phenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 534.2 (M + H^+).	0.018

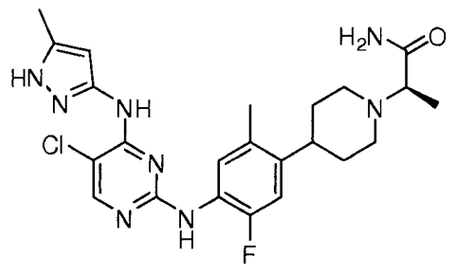
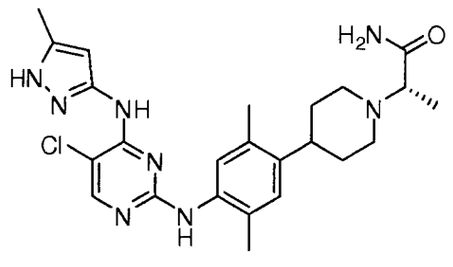
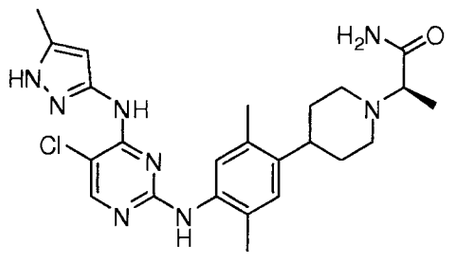
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
146	 5-chloro-N2-(2,5-dimethyl-4-(1-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl))piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS m/z 544.2 (M + H^+).	0.258
147	 5-chloro-N2-(2-chloro-5-methyl-4-(1-(1,1-dioxido-3-thietanyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 536.1 (M + H^+).	0.016
148	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(1,1-dioxido-3-thietanyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS m/z 520.2 (M + H^+). ^{1}H NMR (400 MHz, DMSO-d_6 + 1 drop D_2O) δ 8.02 (s, 1H), 7.37 (s, 1H), 7.02 (s, 1H), 6.23 (s, 1H), 4.28-4.22 (m, 2H), 4.12-4.07 (m, 2H), 3.22-3.18 (m, 1H), 2.95-2.92 (m, 2H), 2.68-2.62 (m, 1H), 2.22 (s, 3H), 2.13 (s, 3H), 2.07-2.01 (m, 2H), 1.71-1.55 (m, 4H).	0.018
149	 5-chloro-N2-(4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS m/z 522.2 (M + H+).	0.955

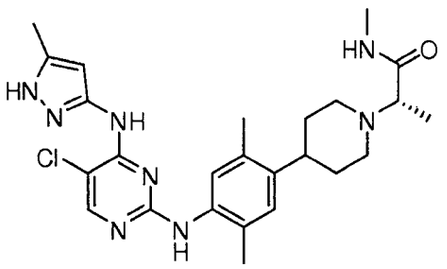
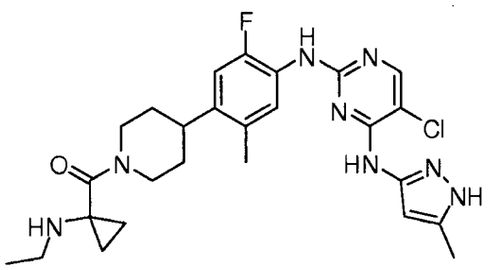
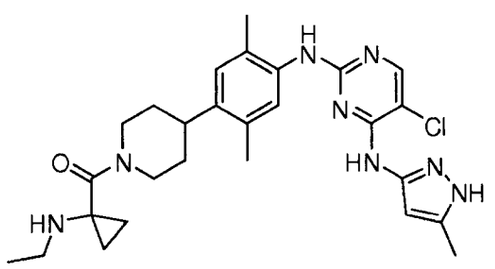
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
150	 5-chloro-N2-(2-fluoro-5-methyl-4-(1,2,3,6-tetrahydropyridin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 414.1 (M + H^+).	0.025
151	 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-2-one	ESMS *m/z* 426.2 (M + H^+).	0.009
152	 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)tetrahydro-2H-pyran-2-one	ESMS *m/z* 427.2 (M + H^+).	0.155
153	 5-chloro-N2-(2-fluoro-4-morpholino-5-(trifluoromethyl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS m/z 472.1 (M + H+).	0.091

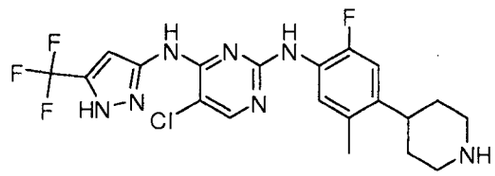
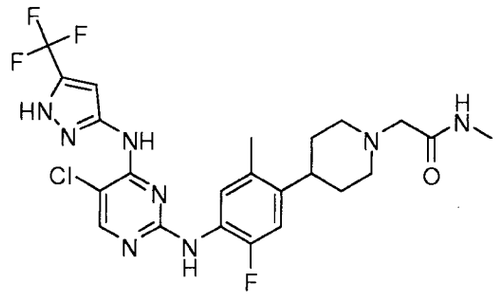
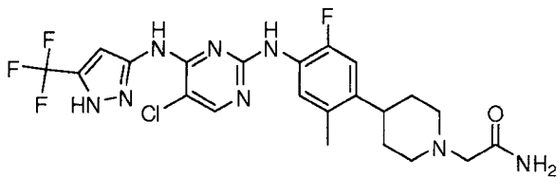
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
154	 5-Chloro-N^2-[4-(1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl)-2,5-dimethyl-phenyl]-N^4-(5-methyl-1*H*-pyrazol-3-yl)-pyrimidine-2,4-diamine	ESMS *m/z* 447.1 (M + H^+).	0.012
155	 1-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperazin-2-one	ESMS *m/z* 427.2 (M + H^+).	1.65
156	 5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)-N2-(2-methyl-4-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)pyrimidine-2,4-diamine	ESMS *m/z* 481.2 (M + H^+)	0.040
157	 5-chloro-N2-(2-fluoro-4-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS m/z 485.2 (M + H^+).	0.075

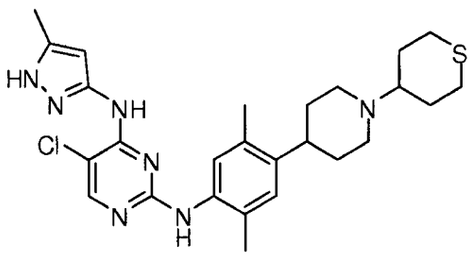
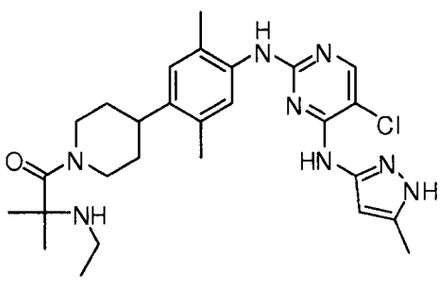
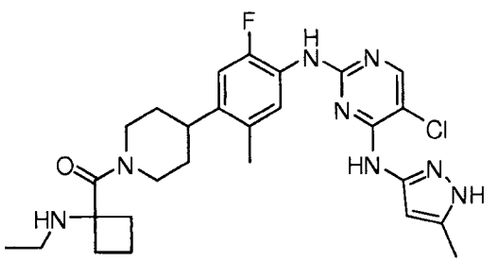
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
158	 3-(5-chloro-2-(2,5-dimethyl-4-(piperidin-4-yl)phenylamino)pyrimidin-4-ylamino)pyridin-2(1H)-one	ESMS *m/z* 425.2 (M + H^+).	0.062
159	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(5-methylisoxazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 431.2 (M + H^+).	0.073
160	 3-(5-chloro-2-(2,5-dimethyl-4-(piperidin-4-yl)phenylamino)pyrimidin-4-ylamino)pyridin-2(1H)-one	ESMS *m/z* 425.2 (M + H^+).	
161	 5-chloro-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 456.2 (M + H^+).	0.332

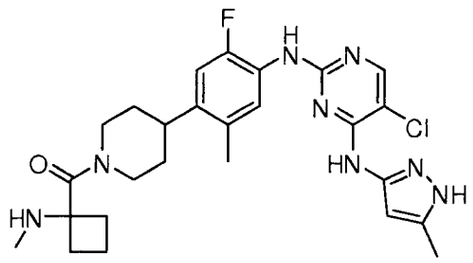
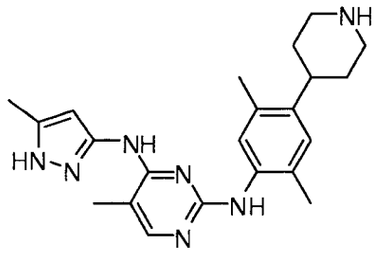
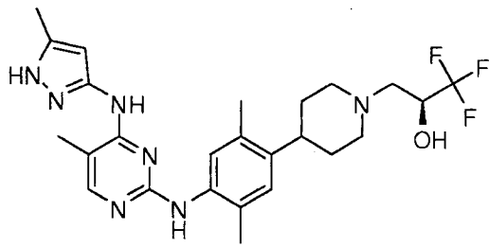
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
162	 ethyl 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidine-1-carboxylate	ESMS *m/z* 438.9 (M + H^+).	0.013
163	 (S)-2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)propanamide	ESMS *m/z* 487.2 (M + H^+)	0.056
164	 (S)-2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-N-methylpropanamide	ESMS *m/z* 501.2 (M + H^+); ^{1}HNMR (MeOD-d_4) δ 8.25 (s, 1H), 7.56 (m, 1H), 7.20 (d, 1H), 6.46 (s, 1H), 3.97 (m, 1H), 3.79 (m, 1H), 3.62 (m, 1H), 3.25 (m, 3H), 2.84 (s, 3H), 2.40 (d, 6H), 2.08 (m, 4H), 1.62 (m, 3H).	0.033

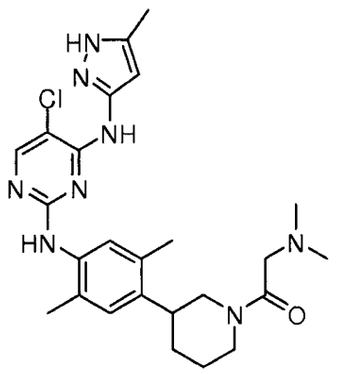
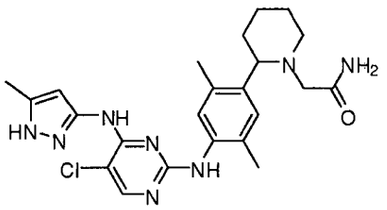
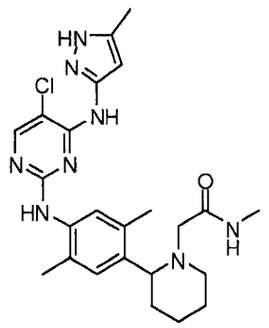
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
165	 (R)-2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)propanamide	ESMS *m/z* 487.2 (M + H^+); ^{1}HNMR (MeOD-d_4) δ 8.22 (s, 1H), 7.61 (t, 1H), 7.18 (d, 1H), 6.40 (s, 1H), 3.79 (m, 1H), 3.65 (m, 1H), 3.54 (m, 1H), 3.22 (m, 3H), 2.39 (d, 6H), 2.08 (m, 4H), 1.66 (d, 3H)	0.038
166	 (S)-2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)propanamide	ESMS *m/z* 483.2 (M + H^+)	0.007
167	 (R)-2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)propanamide	ESMS *m/z* 483.2 (M + H^+)	0.006

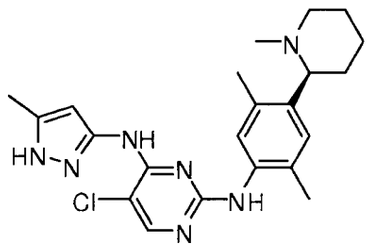
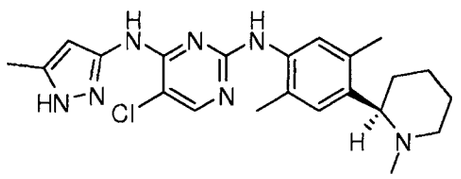
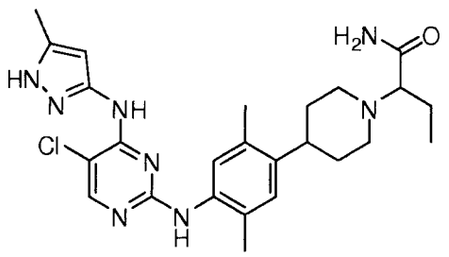
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
168	 (S)-2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylpropanamide	ESMS *m/z* 497.2 (M + H^+)	0.01
169	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-(ethylamino)cyclopropyl)methanone	ESMS *m/z* 527.2 (M + H^+); ^{1}HNMR (MeOD-d_4) δ 8.24 (s, 1H), 7.49 (d, 1H), 7.23 (d, 1H), 6.47 (s, 1H), 4.52 (d, 2H), 3.26 (q, 2H), 3.18 (m, 3H), 2.40 (s, 6H), 1.91(d, 2 H), 1.71(m, 2H), 1.49 (m, 3H), 1.39 (t, 3H).	0.004
170	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)(1-(ethylamino)cyclopropyl)methanone	ESMS *m/z* 523.3 (M + H^+)	0.003

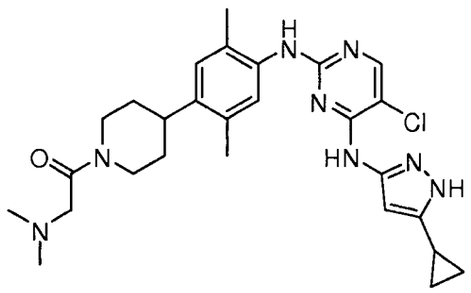
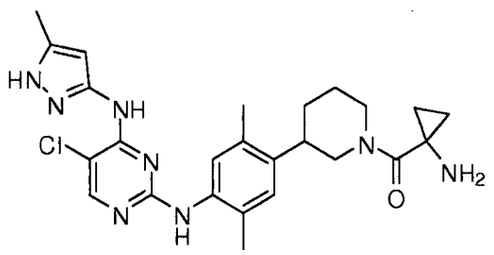
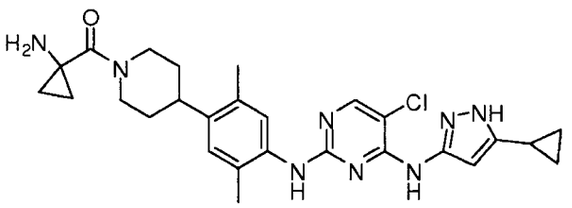
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
171	 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-(trifluoromethyl)-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 470.1 (M + H^+)	0.067
172	 2-(4-(4-(5-chloro-4-(5-(trifluoromethyl)-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-N-methylacetamide	ESMS *m/z* 541.2 (M + H^+)	0.069
173	 2-(4-(4-(5-chloro-4-(5-(trifluoromethyl)-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)acetamide	ESMS *m/z* 527.2 (M + H^+)	0.049

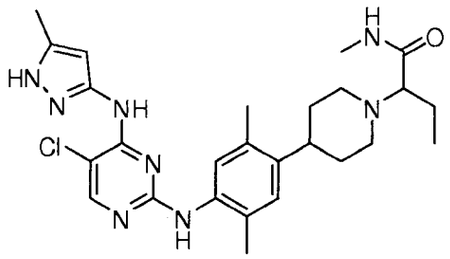
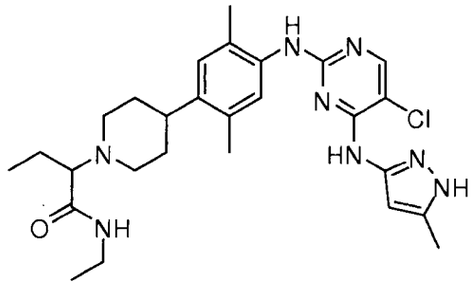
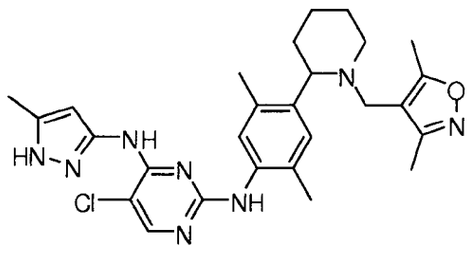
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
174	 5-chloro-N2-(2,5-dimethyl-4-(1-(tetrahydro-2H-thiopyran-4-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 512.2 (M + H^+)	0.008
175	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(ethylamino)-2-methylpropan-1-one	ESMS *m/z* 525.3 (M + H^+)	0.005
176	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-(ethylamino)cyclobutyl)methanone	ESMS *m/z* 541.3 (M + H^+)	0.084

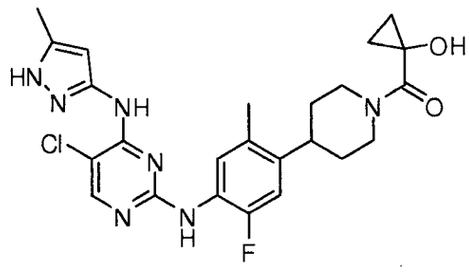
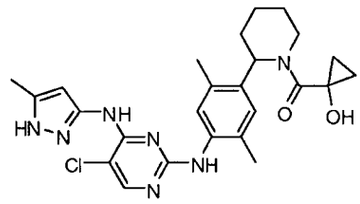
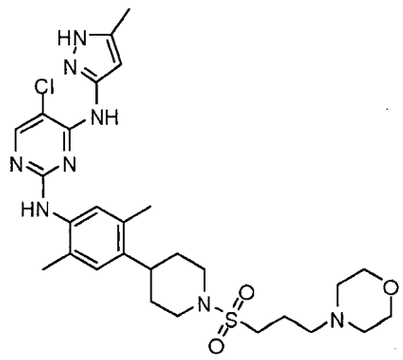
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
177	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-(methylamino)cyclobutyl)methanone	ESMS *m/z* 527.2 (M + H^+)	0.08
178	 N2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-5-methyl-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 392.2 (M + H^+)	3.229
179	 (S)-3-(4-(2,5-dimethyl-4-(5-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)phenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol	ESMS *m/z* 504.3 (M + H^+)	0.12

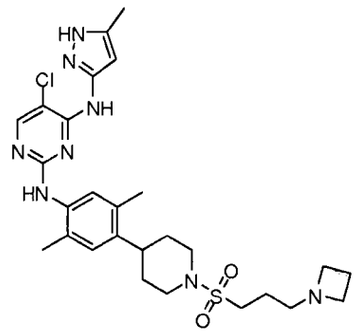
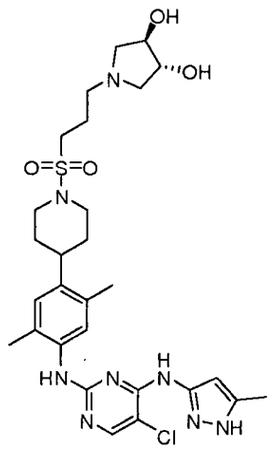
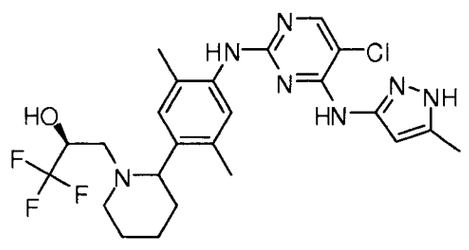
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
180	 1-(3-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone	ESMS *m/z* 497.2 (M + H^+)	0.025
181	 2-(2-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)acetamide	ESMS *m/z* 469.2 (M + H^+)	0.024
182	 2-(2-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide	ESMS *m/z* 483.2 (M + H^+)	0.019

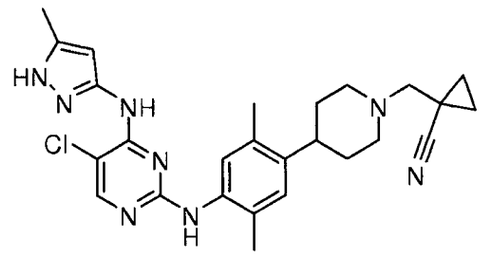
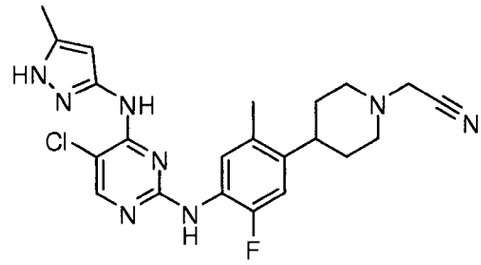
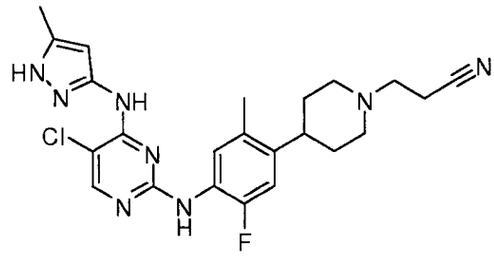
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
183	 (S)-5-chloro-N2-(2,5-dimethyl-4-(1-methylpiperidin-2-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 426.2 (M + H^+)	
184	 (R)-5-chloro-N2-(2,5-dimethyl-4-(1-methylpiperidin-2-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 426.2 (M + H^+)	
185	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)butanamide	ESMS *m/z* 497.2 (M + H^+)	0.009

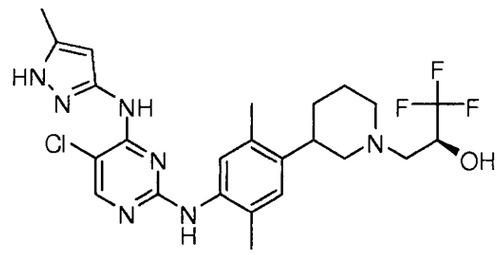
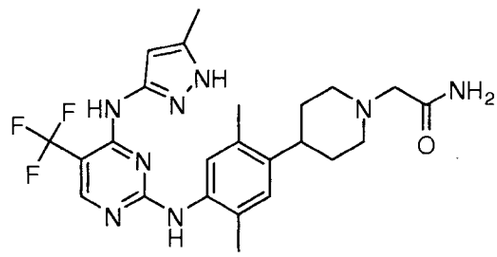
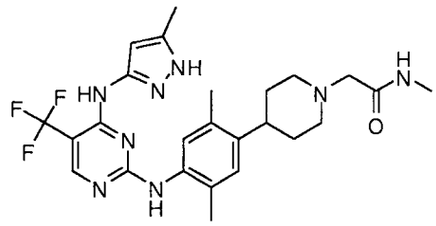
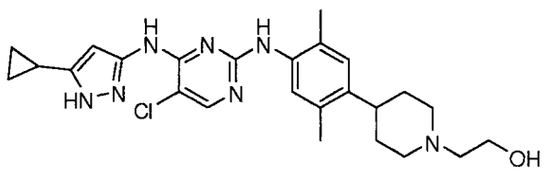
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
186	 1-(4-(4-(5-chloro-4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone	ESMS *m/z* 523.3 (M + H^+)	0.012
187	 (1-aminocyclopropyl)(3-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)methanone	ESMS *m/z* 495.2 (M + H^+)	0.095
188	 (1-aminocyclopropyl)(4-(4-(5-chloro-4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)methanone	ESMS *m/z* 521.2 (M + H^+)	0.019

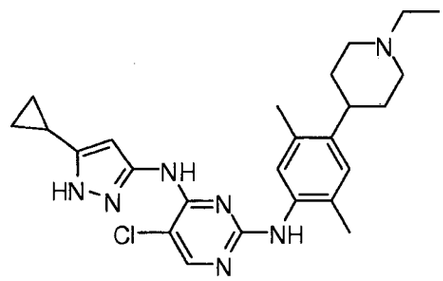
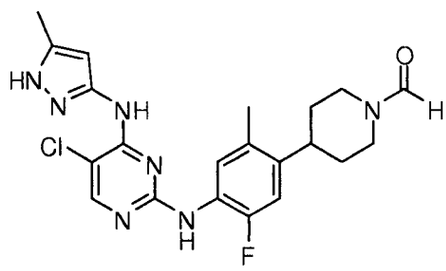
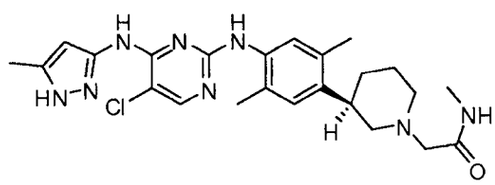
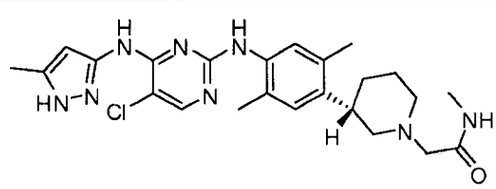
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
189	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylbutanamide	ESMS *m/z* 511.3 (M + H^+)	0.007
190	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-ethylbutanamide	ESMS *m/z* 525.3 (M + H^+)	0.007
191	 5-chloro-N2-(4-(1-((3,5-dimethylisoxazol-4-yl)methyl)piperidin-2-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 521.2 (M + H^+)	0.113

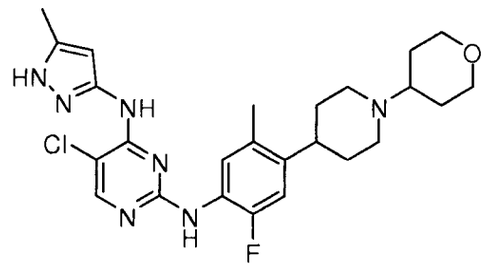
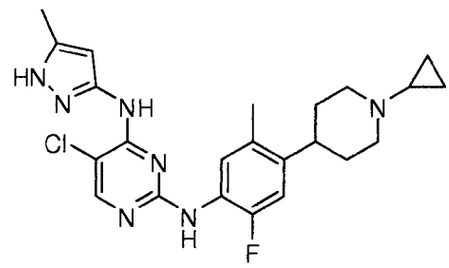
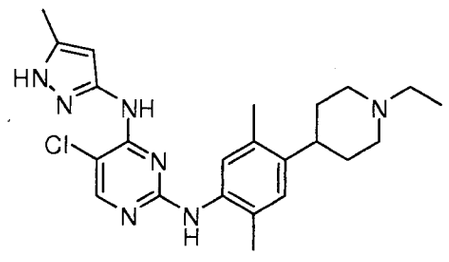
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
192	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-hydroxycyclopropyl)methanone	ESMS *m/z* 500.2 (M + H^+)	0.021
193	 (2-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)(1-hydroxycyclopropyl)methanone	ESMS *m/z* 496.2 (M + H^+)	0.076
194	 5-chloro-N2-(2,5-dimethyl-4-(1-(3-morpholinopropylsulfonyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 603.3 (M + H^+)	0.013

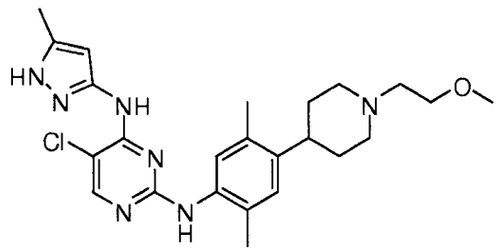
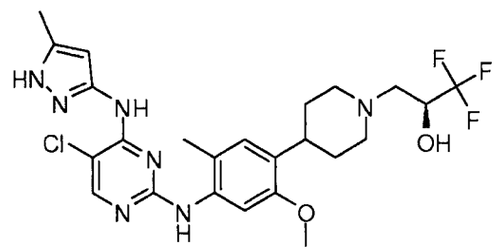
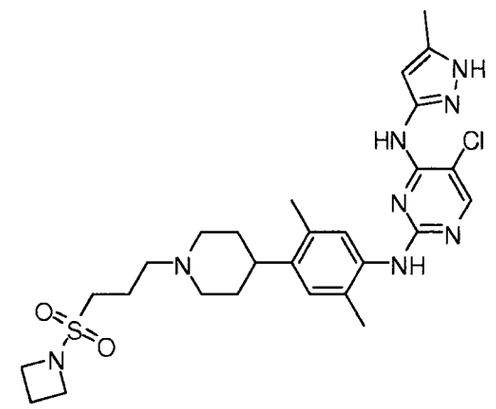
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
195	 N2-(4-(1-(3-(azetidin-1-yl)propylsulfonyl)piperidin-4-yl)-2,5-dimethylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 573.2 (M + H^+)	0.027
196	 (3R,4R)-1-(3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-ylsulfonyl)propyl)pyrrolidine-3,4-diol	ESMS *m/z* 619.3 (M + H^+)	0.37
197	 (2S)-3-(2-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol	ESMS *m/z* 524.2 (M + H^+)	0.21

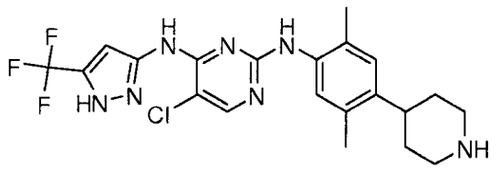
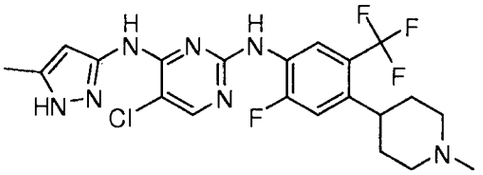
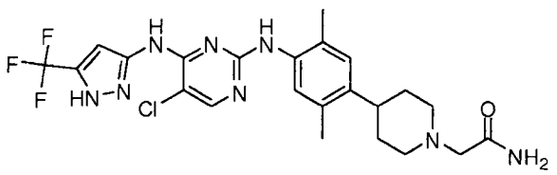
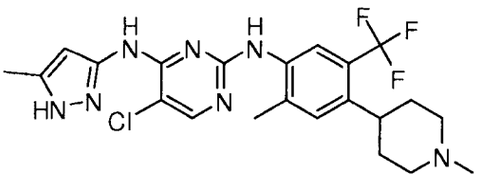
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
198	 1-((4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)methyl)cyclopropanecarbonitrile	ESMS *m/z* 491.2 (M + H^+)	0.022
199	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)acetonitrile	ESMS *m/z* 455.2 (M + H^+)	0.077
200	 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)propanenitrile	ESMS *m/z* 469.2 (M + H^+)	0.036

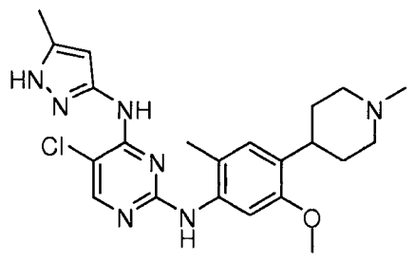
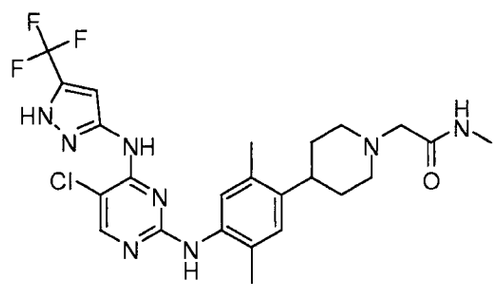
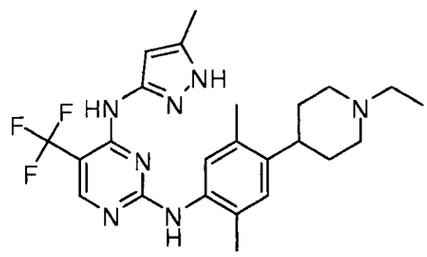
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
201	 (2S)-3-(3-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol	ESMS *m/z* 524.2 (M + H^+)	0.046
202	 2-(4-(2,5-dimethyl-4-(4-(5-methyl-1H-pyrazol-3-ylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)piperidin-1-yl)acetamide	ESMS *m/z* 503.2 (M + H^+); ^{1}HNMR (MeOD-d_4) δ 8.23 (s, 1H), 7.26 (s, 1H), 7.20 (s, 1H), 6.20 (s, 1H), 4.00 (s, 2H), 3.75 (d, 2H), 3.55 (m, 2H), 3.14 (m, 1H), 2.36 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 2.08 (m, 4H).	0.02
203	 2-(4-(2,5-dimethyl-4-(4-(5-methyl-1H-pyrazol-3-ylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)piperidin-1-yl)-N-methylacetamide	ESMS *m/z* 517.3 (M + H^+)	0.015
204	 2-(4-(4-(5-chloro-4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)ethanol	ESMS *m/z* 482.2 (M + H^+)	0.016

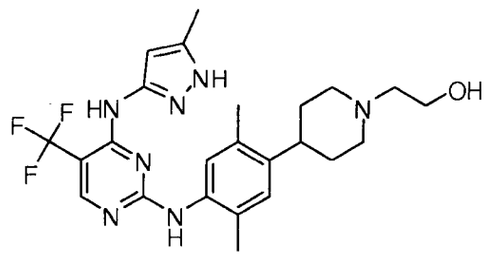
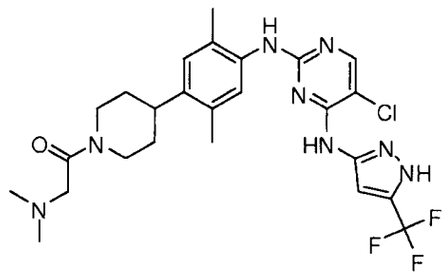
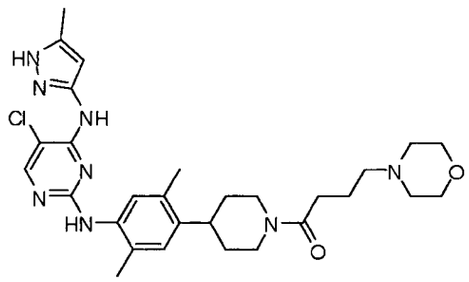
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
205	 5-chloro-N4-(5-cyclopropyl-1H-pyrazol-3-yl)-N2-(4-(1-ethylpiperidin-4-yl)-2,5-dimethylphenyl)pyrimidine-2,4-diamine	ESMS *m/z* 466.2 (M + H^+)	0.019
206	 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidine-1-carbaldehyde	ESMS *m/z* 444.2 (M + H^+)	0.03
207	 (R)-2-(3-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide	ESMS *m/z* 483.2 (M + H^+)	0.026
208	 (S)-2-(3-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide	ESMS *m/z* 483.2 (M + H^+)	0.01

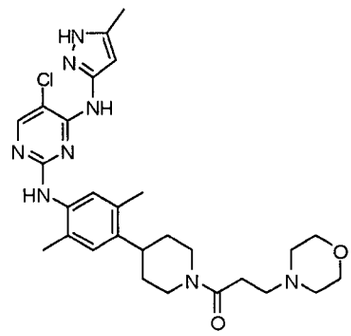
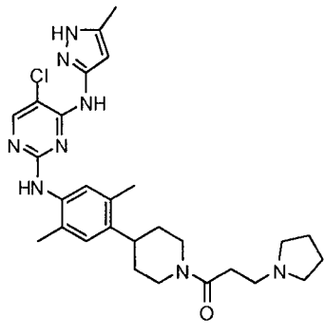
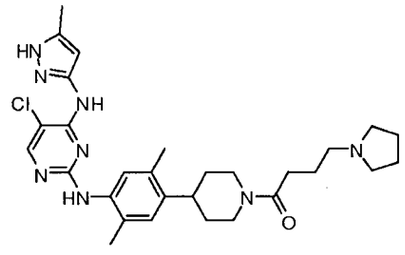
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
209	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 500.2 (M + H^+); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.08 (br, 1H), 9.58 (br, 1H), 8.65 (d, J = 28.4 Hz, 1H), 8.02 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 12.4 Hz, 1H), 6.08 (br, 1H), 3.89 (dd, J = 10.8, 3.6 Hz, 2H), 3.28 (t, J = 10.4 Hz, 2H), 2.99 (d, J = 10.8 Hz, 2H), 2.64-2.43 (m, 2H), 2.24-2.15 (m, 8H), 1.71-1.40 (m, 8H)	0.027
210	 5-chloro-N2-(4-(1-cyclopropylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 456.2 (M + H^+)	0.032
211	 5-chloro-N2-(4-(1-ethylpiperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 440.2 (M + H^+)	0.009

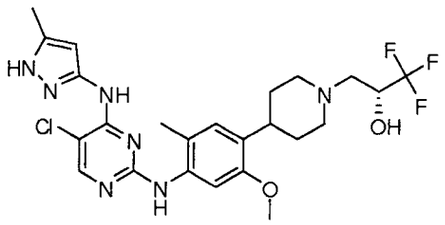
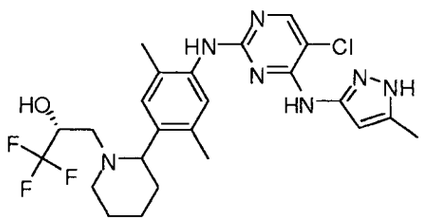
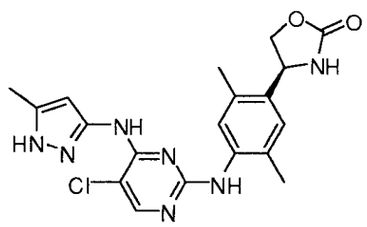
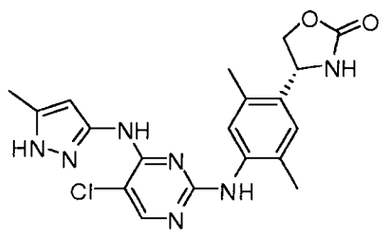
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
212	 5-chloro-N2-(4-(1-(2-methoxyethyl)piperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 470.2 (M + H^+)	0.013
213	 (S)-3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2-methoxy-5-methylphenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol	ESMS *m/z* 540.2 (M + H^+)	0.012
214	 N2-(4-(1-(3-(azetidin-1-ylsulfonyl)propyl)piperidin-4-yl)-2,5-dimethylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 573.2 (M + H^+)	0.04

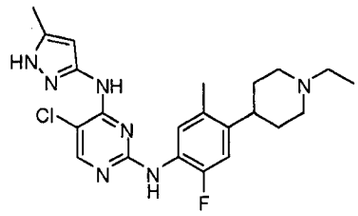
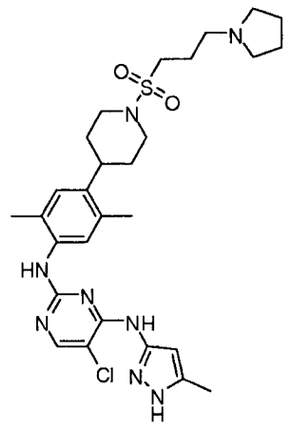
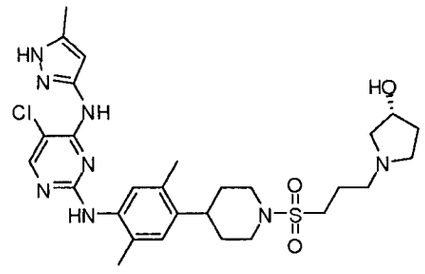
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
215	 5-chloro-N2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-N4-(5-(trifluoromethyl)-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 466.2 (M + H^+)	0.047
216	 5-chloro-N2-(2-fluoro-4-(1-methylpiperidin-4-yl)-5-(trifluoromethyl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 484.2 (M + H^+)	0.047
217	 2-(4-(4-(5-chloro-4-(5-(trifluoromethyl)-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)acetamide	ESMS *m/z* 523.2 (M + H^+)	0.034
218	 5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)-N2-(2-methyl-4-(1-methylpiperidin-4-yl)-5-(trifluoromethyl)phenyl)pyrimidine-2,4-diamine	ESMS *m/z* 480.2 (M + H^+)	0.026

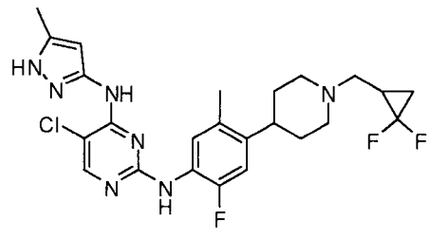
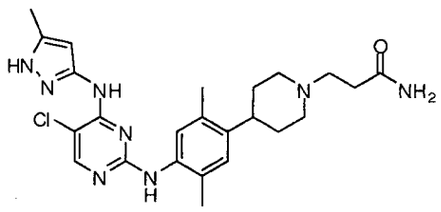
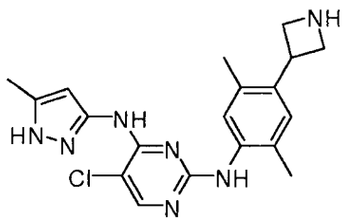
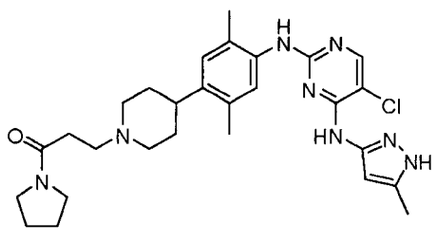
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
219	 5-chloro-N2-(5-methoxy-2-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 442.2 (M + H^+)	0.009
220	 2-(4-(4-(5-chloro-4-(5-(trifluoromethyl)-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide	ESMS *m/z* 537.2 (M + H^+)	0.037
221	 N2-(4-(1-ethylpiperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine	ESMS *m/z* 474.3 (M + H^+)	0.034

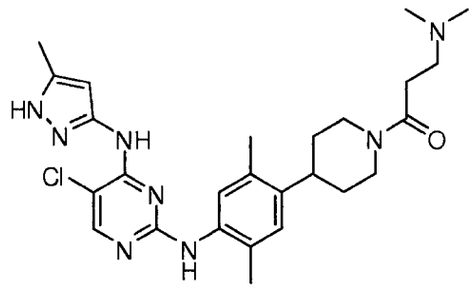
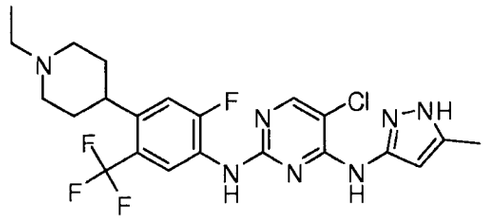
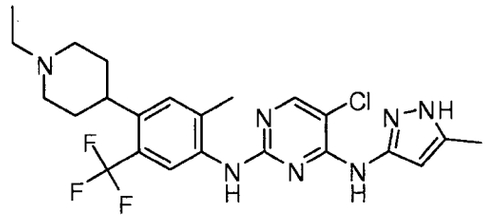
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
222	 2-(4-(2,5-dimethyl-4-(4-(5-methyl-1H-pyrazol-3-ylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)piperidin-1-yl)ethanol	ESMS *m/z* 490.2 (M + H^+)	0.038
223	 1-(4-(4-(5-chloro-4-(5-(trifluoromethyl)-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone	ESMS *m/z* 551.2 (M + H^+)	0.036
224	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-4-morpholinobutan-1-one	ESMS *m/z* 567.3 (M + H^+)	0.02

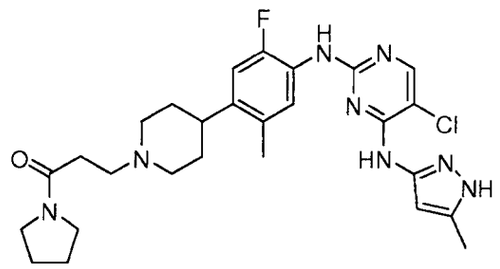
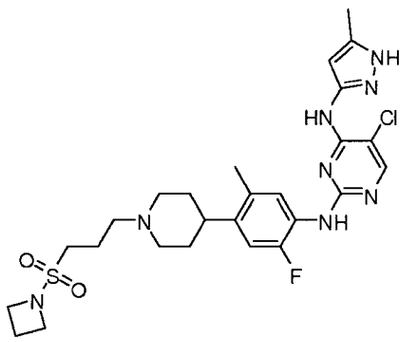
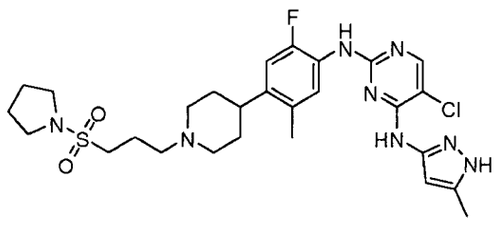
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
225	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-3-morpholinopropan-1-one	ESMS *m/z* 553.3 (M + H^+)	0.017
226	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-3-(pyrrolidin-1-yl)propan-1-one	ESMS *m/z* 537.3 (M + H^+)	0.061
227	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-4-(pyrrolidin-1-yl)butan-1-one	ESMS *m/z* 551.3 (M + H^+)	0.123

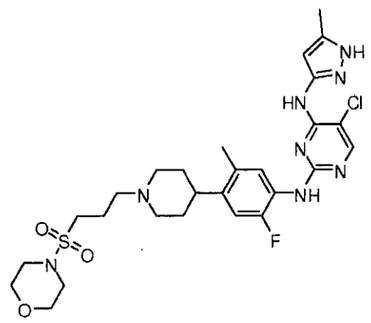
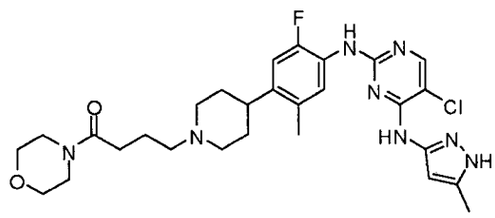
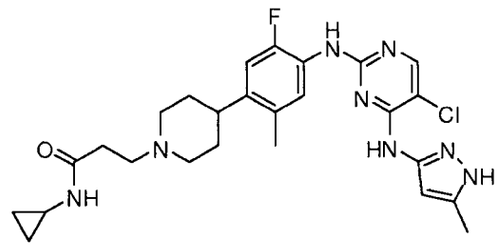
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
228	 (R)-3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2-methoxy-5-methylphenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol	ESMS *m/z* 540.2 (M + H^+)	0.023
229	 (2R)-3-(2-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol	ESMS *m/z* 524.2 (M + H^+)	0.211
230	 (S)-4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)oxazolidin-2-one	ESMS *m/z* 414.1 (M + H^+)	0.04
231	 (R)-4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)oxazolidin-2-one	ESMS *m/z* 414.1 (M + H^+)	0.05

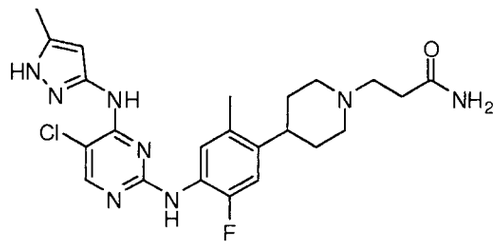
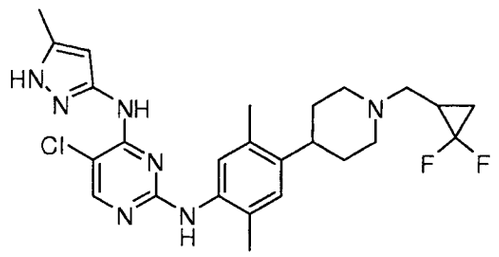
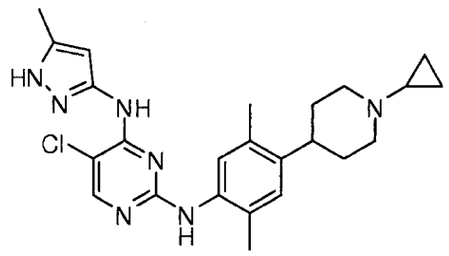
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
232	 5-chloro-N2-(4-(1-ethylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 444.2 (M + H^+); ^{1}HNMR (DMSO-d_6) δ 8.01 (s, 1H), 7.35 (m, 1H), 7.02 (d, 1H), 6.22 (s,1H), 2.97 (d, 2H), 2.62 (m, 1H), 2.34 (q, 2H), 2.21 (s, 3H), 2.13 (s, 3H), 1.98 (t, 2H), 1.64 (m, 4H), 1.01 (t, 3H).	0.020
233	 5-chloro-N2-(2,5-dimethyl-4-(1-(3-(pyrrolidin-1-yl)propylsulfonyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 587.3 (M + H^+)	0.054
234	 (R)-1-(3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-ylsulfonyl)propyl)pyrrolidin-3-ol	ESMS *m/z* 603.3 (M + H^+)	0.073

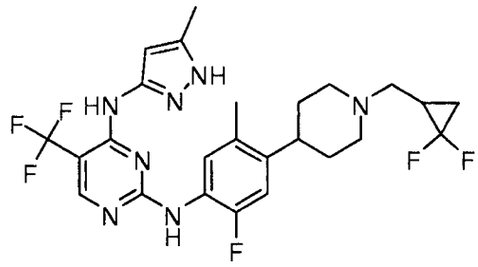
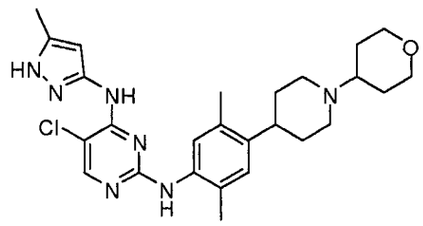
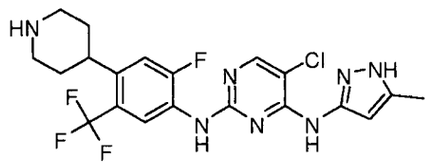
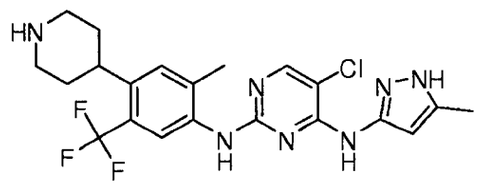
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
235	 5-chloro-N2-(4-(1-((2,2-difluorocyclopropyl)methyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 506.2 (M + H^+)	0.063
236	 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)propanamide	ESMS *m/z* 483.2 (M + H^+)	0.059
237	 N2-(4-(azetidin-3-yl)-2,5-dimethylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 384.2 (M + H^+)	0.41
238	 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-1-(pyrrolidin-1-yl)propan-1-one	ESMS *m/z* 537.3 (M + H^+)	0.039

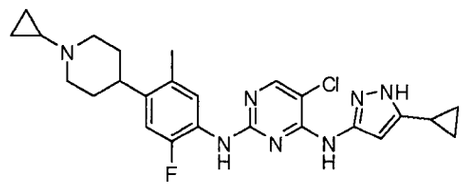
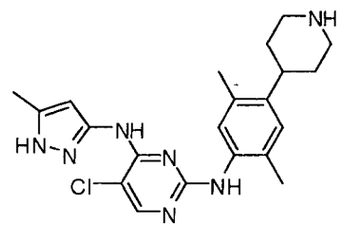
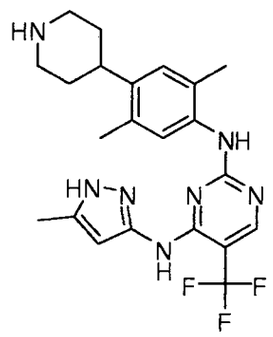
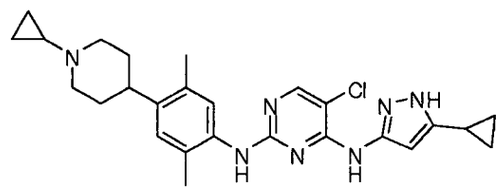
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
239	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-3-(dimethylamino)propan-1-one	ESMS *m/z* 511.3 (M + H^+)	0.073
240	 5-chloro-N2-(4-(1-ethylpiperidin-4-yl)-2-fluoro-5-(trifluoromethyl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 498.2 (M + H^+)	0.102
241	 5-chloro-N2-(4-(1-ethylpiperidin-4-yl)-2-methyl-5-(trifluoromethyl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 494.2 (M + H^+)	0.068

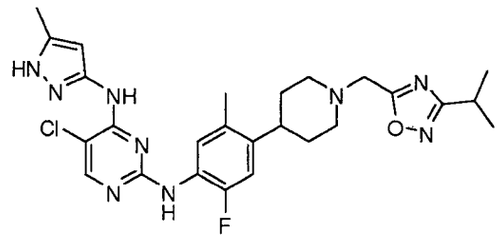
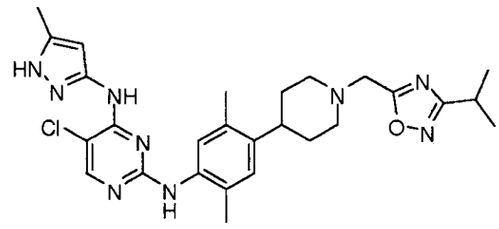
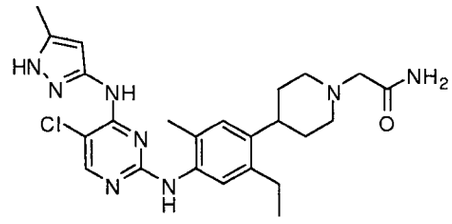
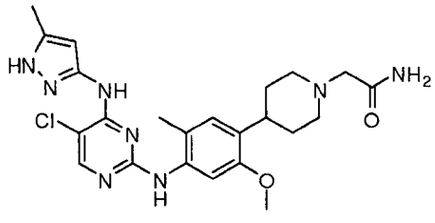
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
242	 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-1-(pyrrolidin-1-yl)propan-1-one	ESMS *m/z* 541.3 (M + H^+)	0.06
243	 N2-(4-(1-(3-(azetidin-1-ylsulfonyl)propyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 577.2 (M + H^+)	0.076
244	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(3-(pyrrolidin-1-ylsulfonyl)propyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 591.2 (M + H^+)	0.084

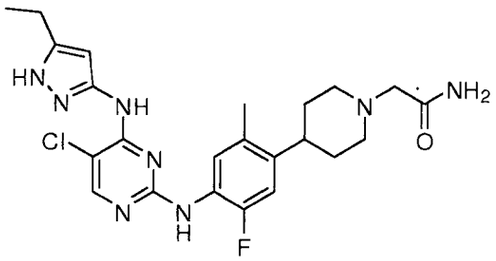
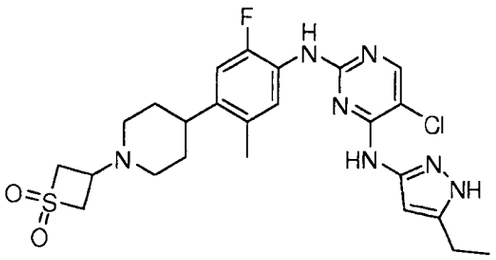
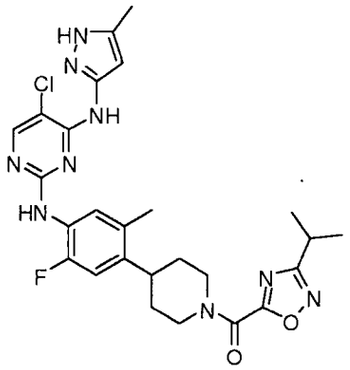
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
245	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(3-(morpholinosulfonyl)propyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 607.2 (M + H^+)	0.077
246	 4-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-1-morpholinobutan-1-one	ESMS *m/z* 571.3 (M + H^+)	0.058
247	 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-N-cyclopropylpropanamide	ESMS *m/z* 527.2 (M + H^+)	0.062

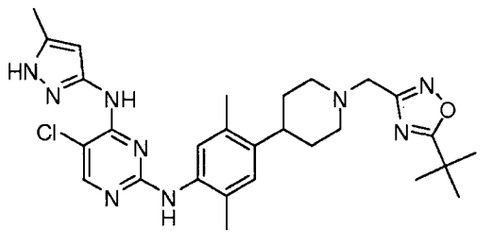
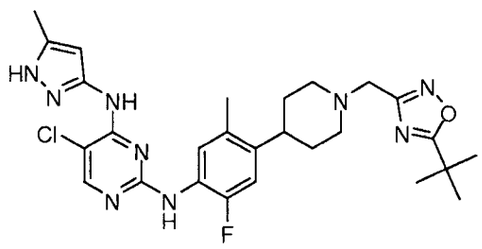
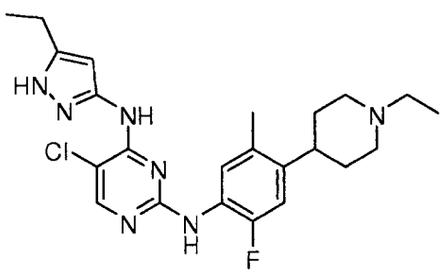
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
248	 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)propanamide	ESMS *m/z* 487.2 (M + H^+)	0.14
249	 5-chloro-N2-(4-(1-((2,2-difluorocyclopropyl)methyl)piperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 502.2 (M + H^+)	0.032
250	 5-chloro-N2-(4-(1-cyclopropylpiperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 452.2 (M + H^+)	0.025

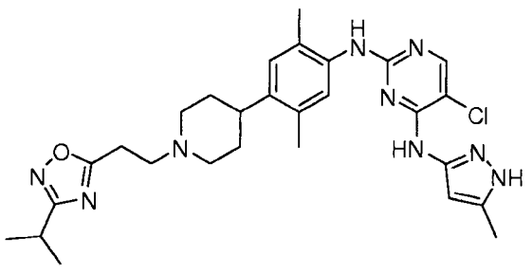
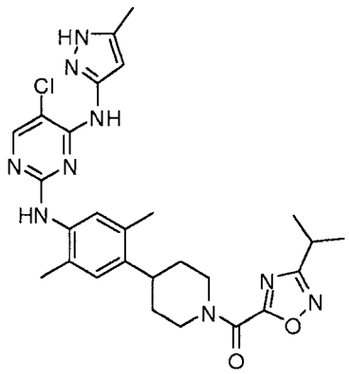
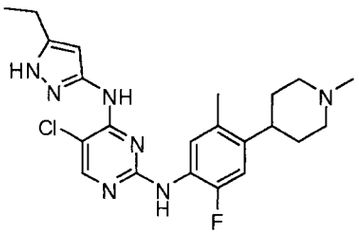
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
251	 N2-(4-(1-((2,2-difluorocyclopropyl)methyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine	ESMS *m/z* 540.2 (M + H^+)	0.052
252	 5-chloro-N2-(2,5-dimethyl-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 496.3 (M + H^+)	0.014
253	 5-chloro-N2-(2-fluoro-4-(piperidin-4-yl)-5-(trifluoromethyl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 470.1 (M + H^+)	0.075
254	 5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)-N2-(2-methyl-4-(piperidin-4-yl)-5-(trifluoromethyl)phenyl)pyrimidine-2,4-diamine	ESMS *m/z* 466.2 (M + H^+)	0.07

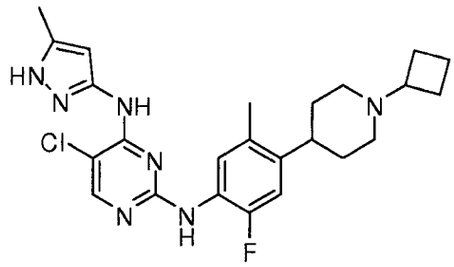
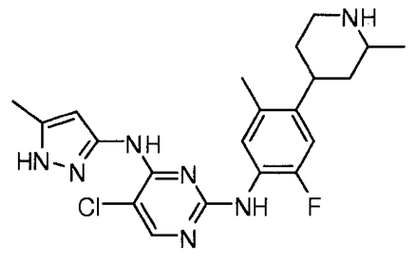
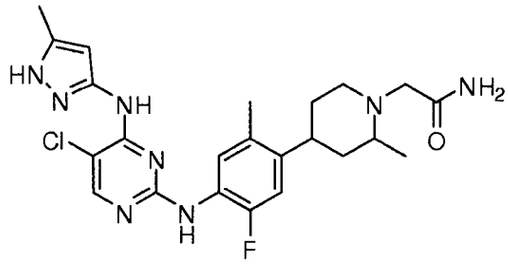
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
255	 5-chloro-N4-(5-cyclopropyl-1H-pyrazol-3-yl)-N2-(4-(1-cyclopropylpiperidin-4-yl)-2-fluoro-5-methylphenyl)pyrimidine-2,4-diamine	ESMS *m/z* 482.2 (M + H^+)	0.228
256	 5-chloro-N2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 412.2 (M + H^+)	0.044
257	 N2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine	ESMS *m/z* 446.2 (M + H^+)	0.064
258	 5-chloro-N4-(5-cyclopropyl-1H-pyrazol-3-yl)-N2-(4-(1-cyclopropylpiperidin-4-yl)-2,5-dimethylphenyl)pyrimidine-2,4-diamine	ESMS *m/z* 478.2 (M + H^+)	0.026

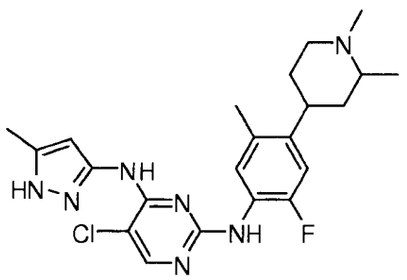
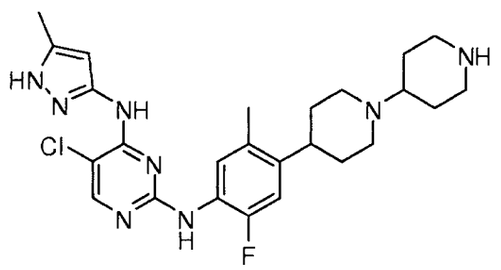
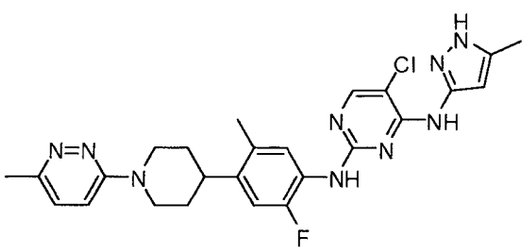
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
259	 5-chloro-N2-(2-fluoro-4-(1-((3-isopropyl-1,2,4-oxadiazol-5-yl)methyl)piperidin-4-yl)-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 540.2 (M + H^+)	0.064
260	 5-chloro-N2-(4-(1-((3-isopropyl-1,2,4-oxadiazol-5-yl)methyl)piperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 536.3 (M + H^+)	0.018
261	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2-ethyl-5-methylphenyl)piperidin-1-yl)acetamide	ESMS *m/z* 483.2 (M + H^+)	0.027
262	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2-methoxy-5-methylphenyl)piperidin-1-yl)acetamide	ESMS *m/z* 485.2 (M + H^+)	0.019

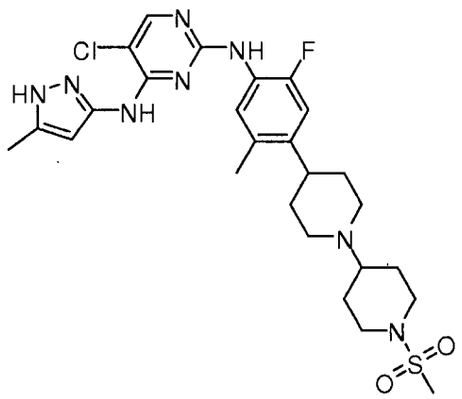
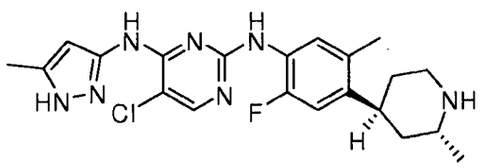
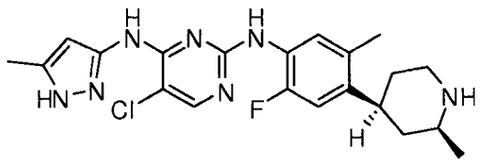
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
263	 2-(4-(4-(5-chloro-4-(5-ethyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)acetamide	ESMS *m/z* 487.2 (M + H^+)	0.033
264	 5-Chloro-N2-{4-[1-(1,1-dioxo-1λ6-thietan-3-yl)-piperidin-4-yl]-2-fluoro-5-methyl-phenyl}-N4-(5-ethyl-1H-pyrazol-3-yl)-pyrimidine-2,4-diamine	ESMS *m/z* 534.2 (M + H^+)	0.021
265	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(3-isopropyl-1,2,4-oxadiazol-5-yl)methanone	ESMS *m/z* 554.2 (M + H^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (br s, 2H), 8.50 (s, 1H), 8.07 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 12.4 Hz, 1H), 6.16 (s, 1H), 5.53 (s, 1H), 3.98 (d, *J* = 13.2 Hz, 1H), 3.34 (dt, *J* = 2.0, 2.8 Hz, 1H), 3.15 (m, 1H), 2.82 (m, 2H), 2.62 (t, *J* = 4.8 Hz, 2H), 2.34 (s, 3H), 2.25 9s, 3H), 1.90 (m, 2H), 1.76 (2 H)	0.091

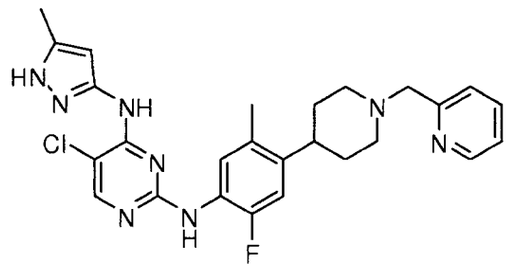
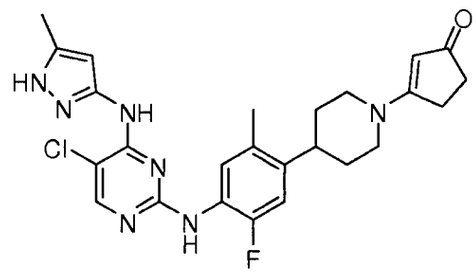
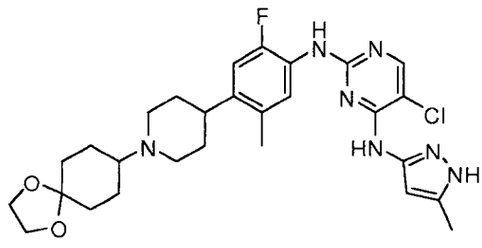
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
266	 N2-(4-(1-((5-tert-butyl-1,2,4-oxadiazol-3-yl)methyl)piperidin-4-yl)-2,5-dimethylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 550.3 (M + H^+)	0.025
267	 N2-(4-(1-((5-tert-butyl-1,2,4-oxadiazol-3-yl)methyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 554.3 (M + H^+)	0.077
268	 5-chloro-N4-(5-ethyl-1H-pyrazol-3-yl)-N2-(4-(1-ethylpiperidin-4-yl)-2-fluoro-5-methylphenyl)pyrimidine-2,4-diamine	ESMS *m/z* 458.2 (M + H^+)	0.022

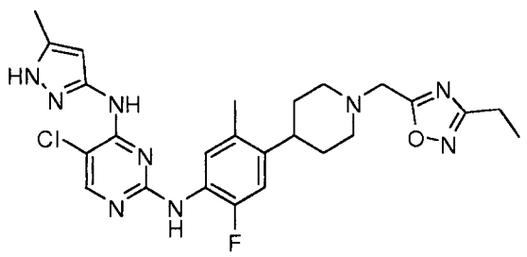
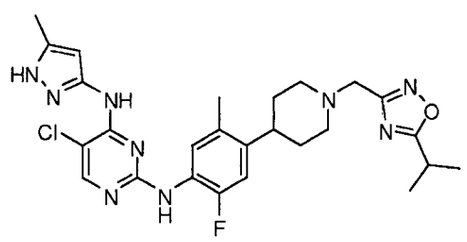
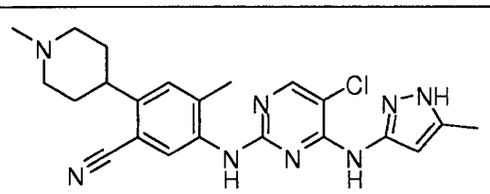
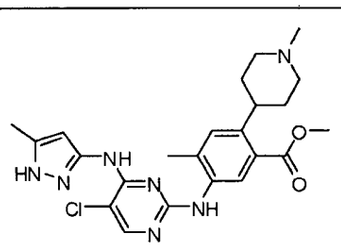
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
269	 5-chloro-N2-(4-(1-(2-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl)piperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 550.3 (M + H^+)	0.039
270	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)(3-isopropyl-1,2,4-oxadiazol-5-yl)methanone	ESMS *m/z* 550.2 (M + H^+)	0.018
271	 5-chloro-N4-(5-ethyl-1H-pyrazol-3-yl)-N2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)pyrimidine-2,4-diamine	ESMS *m/z* 444.2 (M + H^+)	0.013

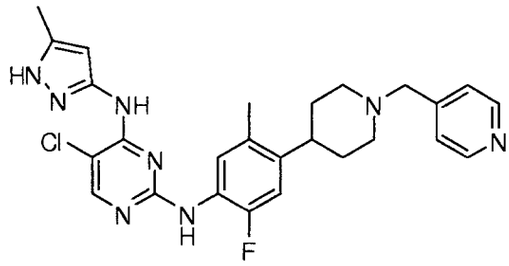
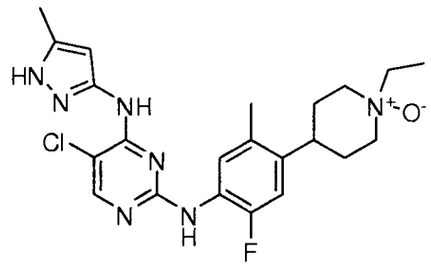
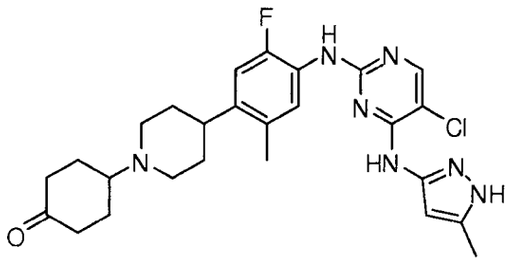
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
272	 5-chloro-N2-(4-(1-cyclobutylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 470.2 (M + H^+)	0.050
273	 5-chloro-N2-(2-fluoro-5-methyl-4-(2-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 430.2 (M + H^+)	0.018
274	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)-2-methylpiperidin-1-yl)acetamide	ESMS *m/z* 487.2 (M + H^+)	0.006

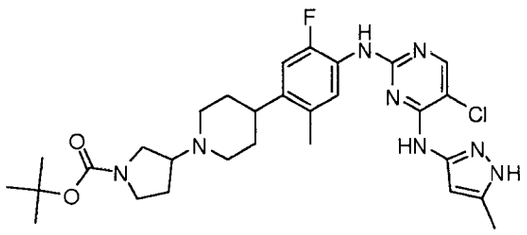
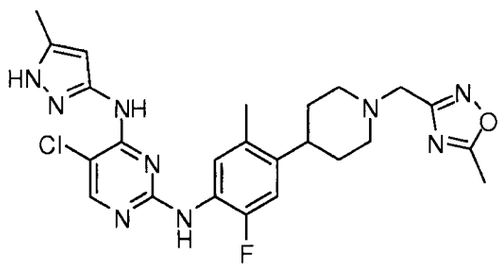
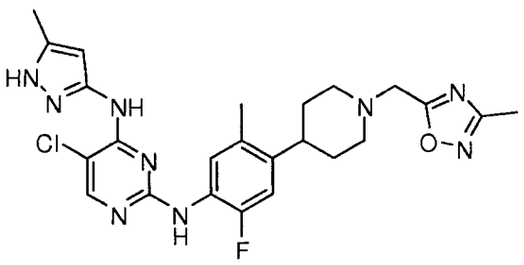
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
275	 5-chloro-N2-(4-(1,2-dimethylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 444.2 (M + H^+)	0.009
276	 N2-(4-(1,4'-bipiperidin-4-yl)-2-fluoro-5-methylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 499.2 (M + H^+)	0.437
277	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(6-methylpyridazin-3-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 508.2 (M + H^+)	0.097

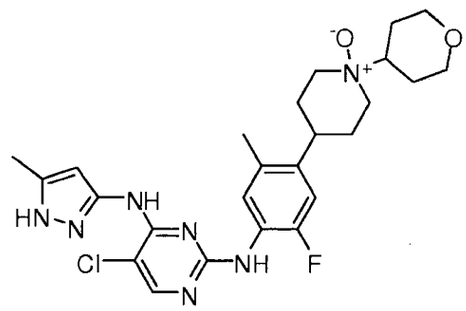
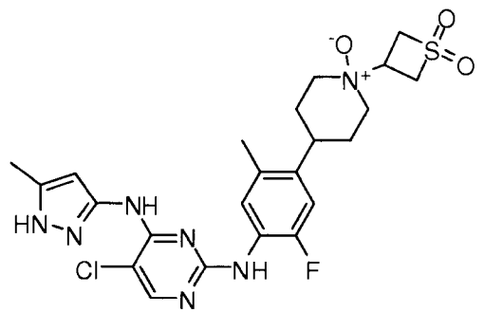
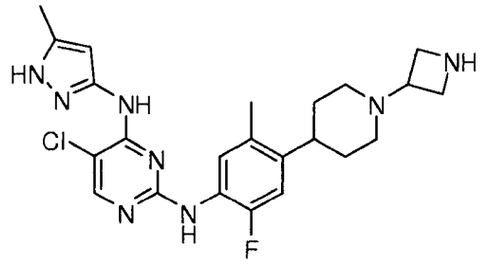
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
278	 5-chloro-N2-(2-fluoro-5-methyl-4-(1'-(methylsulfonyl)-1,4'-bipiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 577.2 (M + H^+)	0.009
279	 5-chloro-N2-(2-fluoro-5-methyl-4-((trans)-2-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 430.2 (M + H^+)	0.064
280	 5-chloro-N2-(2-fluoro-5-methyl-4-((cis)-2-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 430.2 (M + H^+)	0.163

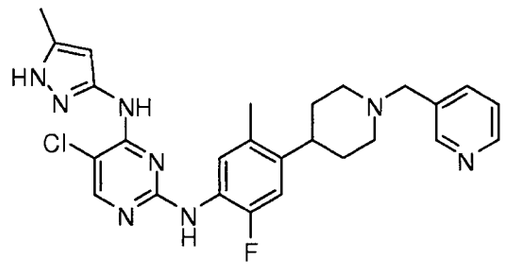
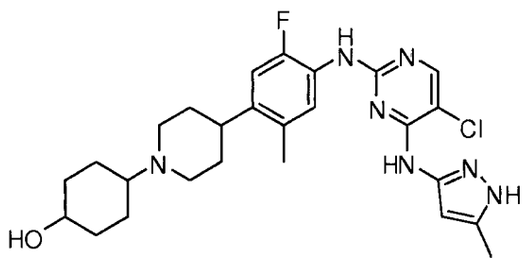
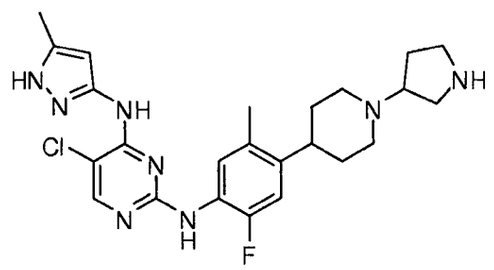
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
281	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(pyridin-2-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 507.2 (M + H^+)	0.087
282	 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)cyclopent-2-enone	ESMS *m/z* 496.2 (M + H^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (br s, 1H), 9.83 (br s, 1H), 8.90 (s, 1H), 8.32 (d, *J* = 6.8 Hz, 1H), 7.88 (d, *J* = 12.8 Hz, 1H), 6.97 (s, 1H), 6.04 (s, 1H), 5.30 (br s, 1H), 4.71 (d, J = 12.0 Hz, 2H), 4.04 (t, *J* = 12.4 Hz, 2H), 3.84 (m, 1H), 3.53 (m, 2H), 3.13 (m, 2H), 3.08 (s, 3H), 2.96 (s, 3H), 2.59-2.40 (m, 4H)	0.048
283	 N2-(4-(1-(1,4-dioxaspiro[4.5]decan-8-yl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 556.3 (M + H^+)	0.016

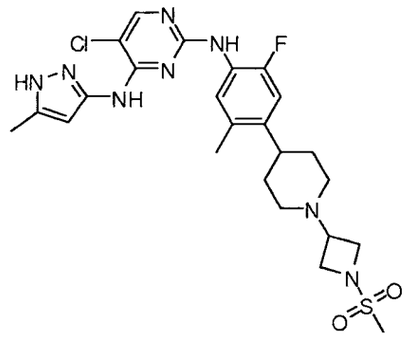
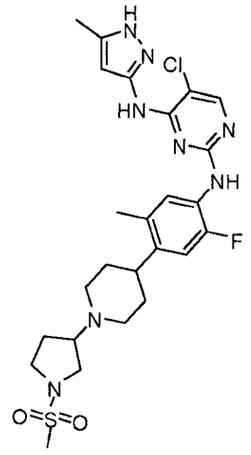
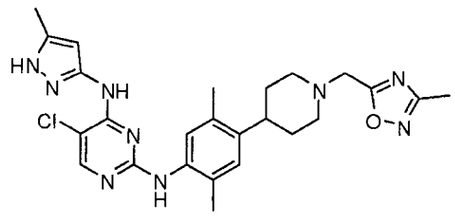
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
284	 5-chloro-N2-(4-(1-((3-ethyl-1,2,4-oxadiazol-5-yl)methyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 526.2 (M + H^+)	0.033
285	 5-chloro-N2-(2-fluoro-4-(1-((5-isopropyl-1,2,4-oxadiazol-3-yl)methyl)piperidin-4-yl)-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 540.2 (M + H^+)	0.068
286	 5-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-4-methyl-2-(1-methylpiperidin-4-yl)benzonitrile	ESMS *m/z* 437.2 (M + H^+)	0.037
287	 methyl 5-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-4-methyl-2-(1-methylpiperidin-4-yl)benzoate	ESMS *m/z* 470.2 (M + H^+)	0.027

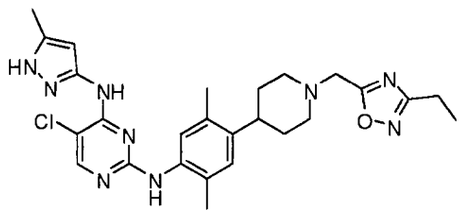
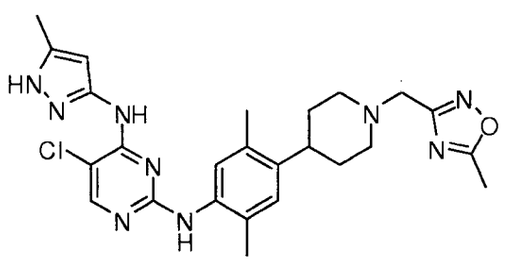
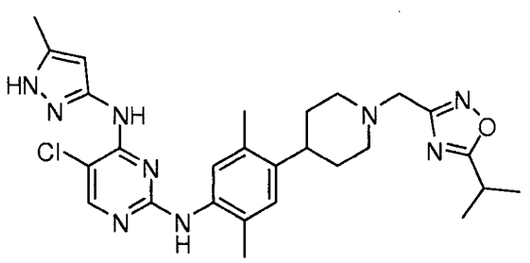
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
288	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(pyridin-4-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 507.2 (M + H^+)	0.093
289	 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)-1-ethylpiperidine 1-oxide	ESMS *m/z* 460.2 (M + H^+); ^{1}HNMR (MeOD-d_4) δ 7.91 (s, 1H), 7.69 (d, 1H), 7.00 (d, 1H), 6.15 (s, 1H), 3.28 (m, 4H), 2.91 (m, 1H), 2.32 (m, 2H), 2.20 (s, 3H), 2.16 (s, 3H), 1.83 (s, 2H), 1.64 (d, 2H), 1.31 (t, 3H).	0.37
290	 4-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)cyclohexanone	ESMS *m/z* 512.2 (M + H^+)	0.023

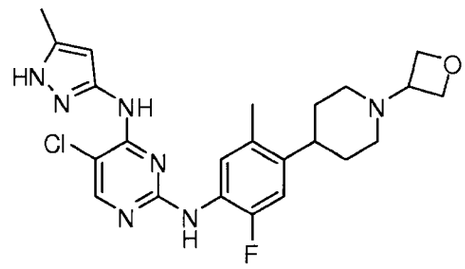
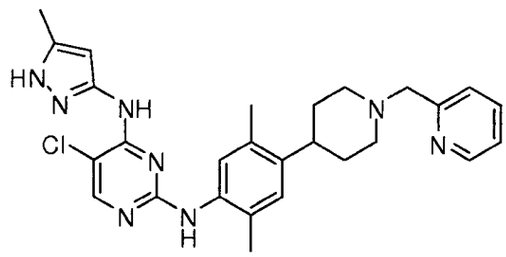
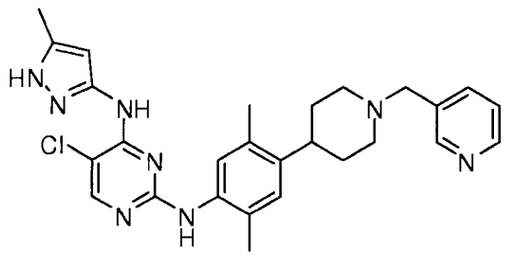
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
291	 tert-butyl 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)pyrrolidine-1-carboxylate	ESMS *m/z* 585.3 (M + H^+)	0.067
292	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-((5-methyl-1,2,4-oxadiazol-3-yl)methyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 512.2 (M + H^+)	0.023
293	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 512.2 (M + H^+)	0.026

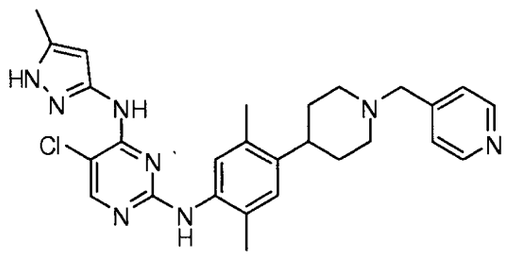
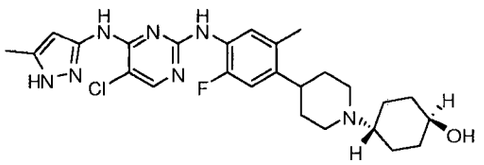
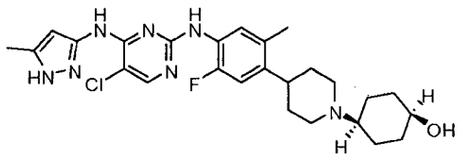
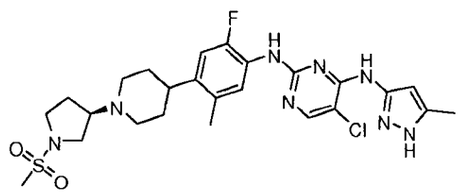
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
294	 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)-1-(tetrahydro-2H-pyran-4-yl)piperidine 1-oxide	ESMS *m/z* 516.2 (M + H^+)	0.064
295	 5-Chloro-N2-{4-[1-(1,1-dioxo-1λ6-thietan-3-yl)-1-oxide-piperidin-4-yl]-2-fluoro-5-methyl-phenyl}-N4-(5-ethyl-1H-pyrazol-3-yl)-pyrimidine-2,4-diamine	ESMS *m/z* 536.2 (M + H^+)	0.039
296	 N2-(4-(1-(azetidin-3-yl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 471.2 (M + H^+)	0.101

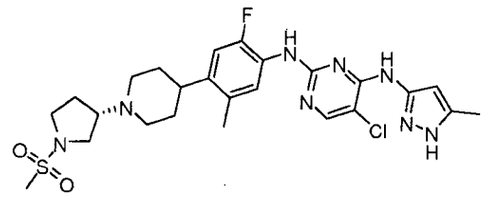
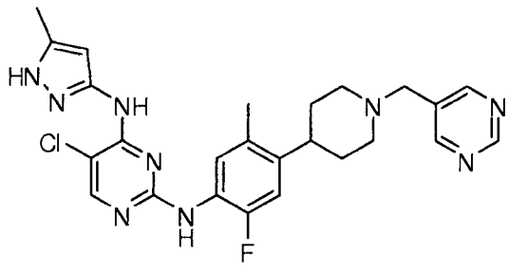
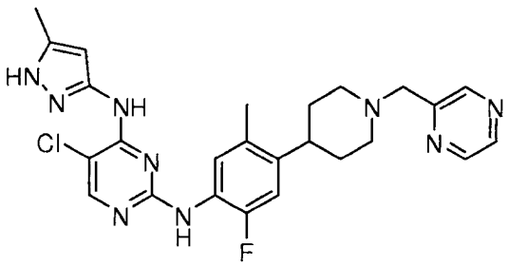
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
297	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(pyridin-3-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 507.2 (M + H^+)	0.079
298	 4-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)cyclohexanol	ESMS *m/z* 514.2 (M + H^+)	0.026
299	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(pyrrolidin-3-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 485.2 (M + H^+)	0.101

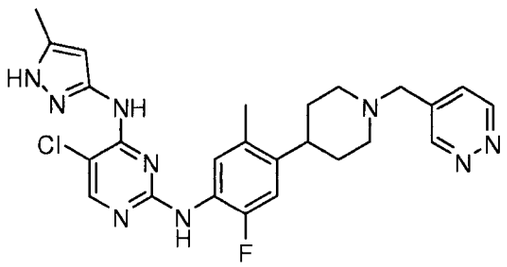
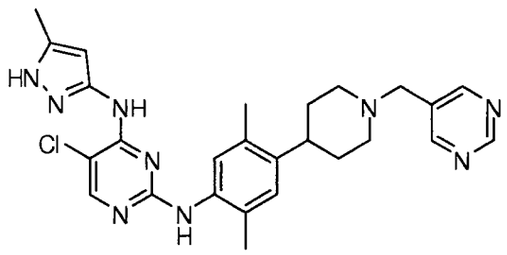
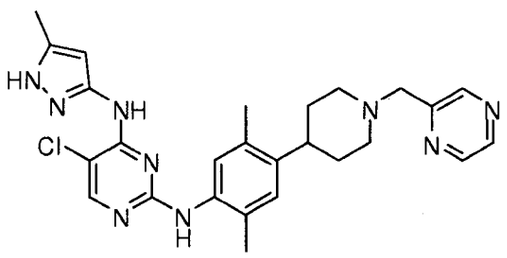
	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
300	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(1-(methylsulfonyl)azetidin-3-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 549.2 (M + H^+)	0.032
301	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(1-(methylsulfonyl)pyrrolidin-3-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 563.2 (M + H^+)	0.038
302	 5-chloro-N2-(2,5-dimethyl-4-(1-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 508.2 (M + H^+)	0.006

	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
303	 5-chloro-N2-(4-(1-((3-ethyl-1,2,4-oxadiazol-5-yl)methyl)piperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 522.2 (M + H^+)	0.006
304	 5-chloro-N2-(2,5-dimethyl-4-(1-((5-methyl-1,2,4-oxadiazol-3-yl)methyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 508.2 (M + H^+)	0.005
305	 5-chloro-N2-(4-(1-((5-isopropyl-1,2,4-oxadiazol-3-yl)methyl)piperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 536.3 (M + H^+)	0.025

	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
306	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(oxetan-3-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 472.2 (M + H^+)	0.015
307	 5-chloro-N2-(2,5-dimethyl-4-(1-(pyridin-2-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 503.2 (M + H^+)	0.007
308	 5-chloro-N2-(2,5-dimethyl-4-(1-(pyridin-3-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 503.2 (M + H^+)	0.006

	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
309	 5-chloro-N2-(2,5-dimethyl-4-(1-(pyridin-4-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 503.2 (M + H^+)	0.008
310	 Trans-4-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)cyclohexanol	ESMS *m/z* 514.2 (M + H^+)	0.027
311	 Cis-4-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)cyclohexanol	ESMS *m/z* 514.2 (M + H^+)	0.021
312	 (R)-5-chloro-N2-(2-fluoro-5-methyl-4-(1-(1-(methylsulfonyl)pyrrolidin-3-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS m/z 563.2 (M + H+)	0.025

	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
313	 (S)-5-chloro-N2-(2-fluoro-5-methyl-4-(1-(1-(methylsulfonyl)pyrrolidin-3-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 563.2 (M + H^+)	0.030
314	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(pyrimidin-5-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 508.2 (M + H^+); ^{1}H NMR (400 MHz, CD_3OD) δ 9.09 (s, 1H), 8.81 (s, 2H), 8.00 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 13.2 Hz, 1H), 6.23 (br s, 1H), 3.65 (s, 2H), 3.03 (m, 2H), 2.76 (m, 1H), 2.27 (s, 3H), 2.25 (s, 3H), 2.25 (m, 2H), 1.80-1.68 (m, 4H)	0.037
315	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(pyrazin-2-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 508.2 (M + H^+)	0.036

	STRUCTURE	NMR or ESMS	IGF-1R Ba/F3 IC50 (uM)
316	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(pyridazin-4-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 508.2 (M + H^+)	0.027
317	 5-chloro-N2-(2,5-dimethyl-4-(1-(pyrimidin-5-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 504.2 (M + H^+)	0.004
318	 5-chloro-N2-(2,5-dimethyl-4-(1-(pyrazin-2-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	ESMS *m/z* 504.2 (M + H^+)	0.010

Assays

[0207] The IC_{50} of a drug may be determined constructing a dose-response curve and examining the effect of different concentrations of antagonist on reversing agonist activity. IC_{50} values may be calculated for a given antagonist by determining the concentration needed to inhibit half of the maximum biological response of the agonist. To calculate IC_{50} values, a series of dose-response data (e.g., drug concentrations x1, x2, ...,xn and growth inhibition y1, y2, ...,yn, the values of y are in the range of 0-1) is generated. IC_{50} values may be determined by a computer-aided system using the formula:

$$y = D+((A-D)/(1+10^{(x-\log(IC50)B)})$$

where A is the ratio of growth inhibition between lowest drug concentration and control; B is the slope of sigmoidal curvel; and D is the ratio of growth inhibition between highest drug concentration and control.

[0208] The IC_{50} value is given as that concentration of the test compound that results in growth inhibition 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 IGF-1R at 10 μM.

Ba/F3 cell line panel and reagents

[0209] 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 TEL-fusion kinase and subjected to puromycin selection and IL-3 withdrawal to obtain IL-3-independent, transformed Ba/F3 cells.

[0210] 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

[0211] 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% CO_2) for 48 hours. 25 μL Britelite (Perkin Elmer) is added and luminescence is quantified using Analyst GT (Molecular Devices). 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.

Enzymatic HTRF assay

[0212] IGF-1R and INSR (insulin receptor) are purchased from Upstate. Following reagents are prepared in-house; 10 x kinase 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.

[0213] 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 Devices).

Cancer cell proliferation inhibition assay

[0214] For luciferizing cancer cell line, each cell line is transduced by ampholytic retrovirus carrying both luciferase gene and puromycin-resistant gene whose expression is driven by LTR. Briefly, the retroviral vector pMSCV-Puro-Luc is transfected into Phoenix cell line using Fugene6 (Roche) according to manufacturer's instruction. Two days after transfection, supernatant containing virus is harvested and filtered with 0.2 μm filter. Harvested virus is used immediately or stored at -80'C. For infection, cultured cancer cells are harvested and plated ($5x10^5$ cells/well in 1 ml medium) on 6-well tissue culture plate. For each well, 3ml virus supernatant is added together with 400 μl FBS, 40 μl 1 M HEPES (pH8.0) and 4 μl of polybrene (10μg/ml, Specialty media). The plate is centrifuged down for 90 minutes at 2500 rpm for spin-infection and is transferred into an incubator for overnight infection. Next day, infected cell line is transferred into T-75 flask containing fresh medium and incubated for one day. Two days after infection, puromycin is added at the final concentration of 1μg/ml to begin selection. Within 1-2 weeks, puromycin-resistant cell line is established after at least two subsequent splits and is preserved as luciferized stock.

[0215] Each cell line is harvested while in log phase growth by trypsinization and diluted in respective media to appropriate density prior to plating. Cells are dispensed using μFill (BioTeK) at 50μl/well into white walled clear bottom plates (Greiner – custom for GNF). Cells are then placed in 37 °C incubator supplying 5% CO2 overnight. Compounds are transferred using 50nL/well Pintool technology via

Platemate (Matrix). Assay plates are then placed back into the incubator for 3 days. On the third day following compound transfer, BRITELITE® (Perkin Elmer, diluted according to manufacturer's suggestion) is added to assay plates and read on Analyst GT (Molecular Devices) or Envision (Perkin Elmer). Raw data is generated in RLU.

Tumor Activity of Exemplary Compounds

[0216] Three to 4 x 10^6 human neuroblastoma SK-N-MC cells resuspended in HBSS and mixed in 50% matrigel were injected subcutaneously (0.05 ml/mouse) into female nude (HsdNpa:athymic/nu) mice 10-12 weeks of age. Treatments were initiated when the mean tumor volumes were approximately 150-200 mm^3. Body weights and tumor volumes were recorded three times a week. Tumor volumes were measured with calipers and determined according to the formula length × $diameter^2$ × $\pi/6$. In addition to presenting fractional changes of tumor volumes over the course of treatments, antitumor activity is expressed as T/C % (mean change of tumor volume of treated animals/mean change of tumor volume of control animals) × 100. Efficacy of test compounds was determined by initiating oral dosing on day 19 post-cell injection following randomization of the mice so that each group has similar mean tumor size. Dosing with an appropriate schedule continued for 7 days based on the general health condition of the animals. All test compounds were formulated in NMP/PEG300 (10:90) and applied daily by gavage. Vehicle consisted of NMP/PEG300 (10:90). All application volumes were 5 ml/kg. The activity of exemplary compounds of the invention on tumor growth is shown in Tables 2-4.

Table 2

	Tumor response			
Treatment	**T/C (%)**	**Regr. (%)**	**Δ tumor volume (mean mm^3 ± SEM)**	**Mean fold change in tumor growth**
NMP/PEG300 (10/90) 5 ml/kg po q8/16h	**100**	**0**	**334 ± 59**	**3.1 ± 0.3**
Test Compound 1 20 mg/kg, q8/16h, po	**53**	**-**	**231 ± 145**	**2.1 ± 0.4**
Test Compound 1 40 mg/kg, q8/16h, po	**35**	**-**	**107 ± 48***	**1.7 ± 0.2***

Table 3

	Tumor response			
Treatment	**T/C (%)**	**Regr. (%)**	**Δ tumor volume (mean mm^3 ± SEM)**	**Mean fold change in tumor growth**
NMP/PEG300 (10/90) 5 ml/kg po q8/16h	**100**	**0**	**334 ± 59**	**3.1 ± 0.3**
Test Compound 2 12.5 mg/kg, q8/16h, po	**69**	**-**	**232 ± 103**	**2.5 ± 0.4**
Test Compound 2 25 mg/kg, q8/16h, po	**22**	**-**	**42 ± 10***	**1.5 ± 0.2***

Table 4

	Tumor response			
Treatment	**T/C (%)**	**Regr. (%)**	**Δ tumor volume (mean mm^3 ± SEM)**	**Mean fold change in tumor growth**
NMP/PEG300 (10/90) 5 ml/kg po q8/16h	**100**	**0**	**334 ± 59**	**3.1 ± 0.3**
Test Compound 3 12.5 mg/kg, q8/16h, po	**58**	**-**	**220 ± 67**	**2.2 ± 0.3**
Test Compound 3 25 mg/kg, q8/16h, po	**26**	**-**	**102 ± 40***	**1.6 ± 0.3***

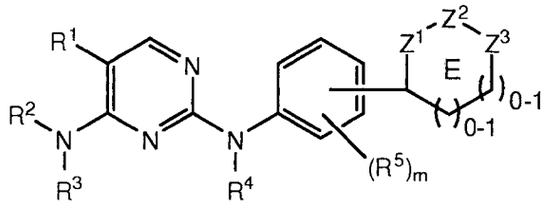
* p< 0.05 vs. Vehicle controls – ANOVA on ranks and post hoc Dunnett's test.

*****

[0217] 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 of Formula (1):



(1)

or a physiologically acceptable salt thereof;

wherein ring E may optionally contain a double bond;

one of Z^1, Z^2 and Z^3 is NR^6, $N(R^6)^+$-O^- or $S(O)_{1-2}$ and the others are CR_2;

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

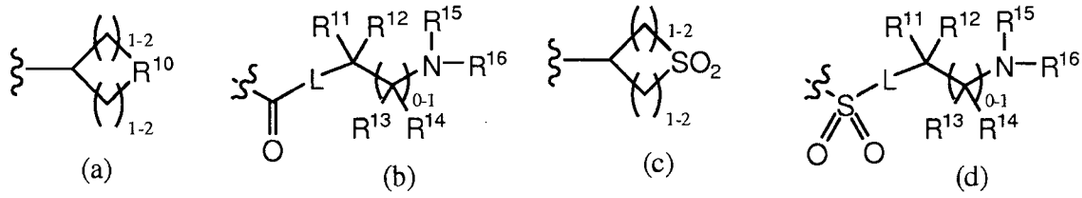
R^2 is pyridine-2-onyl, azepan-2-onyl or a monocyclic 5-6 membered heteroaryl having 1-3 heteroatoms selected from N, O and S; each of which is optionally substituted substituted with R^9 wherein R^9 is C_{1-6} alkyl, C_{1-6} haloalkyl or C_{3-7} cycloalkyl;

R^3 and R^4 are each H;

R^5 is halo, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted C_{1-6} alkyl, halo-substituted C_{1-6} alkoxy, cyano or $C(O)O_{0-1}R^8$;

R^6 is H; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo and/or hydroxyl groups; -$(CR_2)_p$-OR^7, -$(CR_2)_p$-$CH(OH)C_tF_{2t+1}$ wherein t is 1-3, $(CR_2)_p$-CN; $(CR_2)_p$-$NR(R^7)$, -$(CR_2)_p$–$C(O)OR^7$, $(CR_2)_pNR(CR_2)_pOR^7$,
$(CR_2)_pNR$-L-$C(O)R^8$, $C(O)(CR_2)_qOR^8$, -$C(O)O$-$(CR_2)_p$-NRR^7, –C(O) -$(CR_2)_p$-OR^7, L-Y,
-L-$C(O)R^7$, -L–C(O)-NRR^7, -L–C(O)-NR-$(CR_2)_p$-NRR^7,-L-$C(O)NR(CR_2)_pOR^7$,
-L–C(O)-$(CR_2)_q$-NR-C(O)-R^8, -L-$C(O)NR(CR_2)_pSR^7$, -L-$C(O)NR(CR_2)_pS(O)_{1-2}R^8$,
-L-$S(O)_2R^8$, -L-$S(O)_2$-$(CR_2)_q$-NRR^7, -L-$S(O)_2NR(CR_2)_pNR(R^7)$ or
-L-$S(O)_2NR(CR_2)_pOR^7$;

alternatively, R^6 is a radical selected from formula (a), (b), (c) or (d):



R^{10} is O, S, NR^{17} wherein R^{17} is H, C_{1-6} alkyl, SO_2R^{8a} or CO_2R^{8a};

R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are independently selected from H; C_{1-6} alkoxy; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino or hydroxyl groups; or R^{11} and R^{12}, R^{12} and R^{15}, R^{15} and R^{16}, R^{13} and R^{14}, or R^{13} and R^{15} together with the atoms to which they are attached may form a 3-7 membered saturated, unsaturated or partially unsaturated ring containing 1-3 heteroatoms selected from N, O and S, and optionally substituted with oxo and 1-3 R^5 groups;

L is $(CR_2)_{1-4}$ or a bond;

Y is C_{3-7} carbocyclic ring, C_{6-10} aryl, or a 5-10 membered heteroaryl or 4-10 membered heterocyclic ring, each of which is optionally substituted with 1-3 R^5 groups;

R^7, R^8 and R^{8a} are independently C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino, hydroxyl or cyano; $(CR_2)_qY$ or C_{1-6} alkoxy; or R^7 is H;

each R is independently H or C_{1-6} alkyl;

R and R^7 together with N in each NRR^7 may form a 5-6 membered ring containing 1-3 heteroatoms selected from N, O and S, and optionally substituted with oxo and 1-3 R^5 groups;

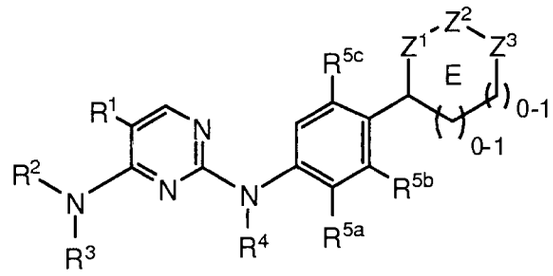
m is 2-4;

n is 1-3;

p is 1-4; and

q is 0-4.

2. The compound of claim 1, wherein said compound is of Formula (2):



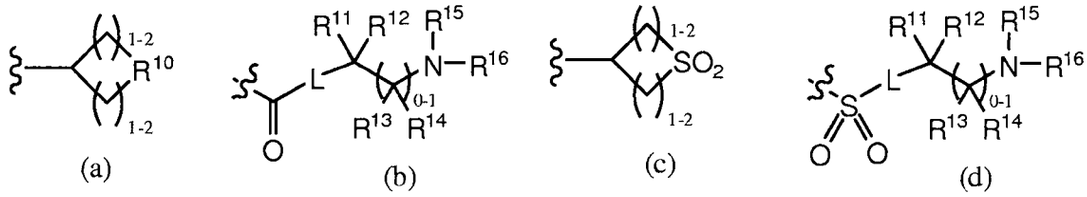
(2)

wherein one of R^{5a}, R^{5b} and R^{5c} is H and the others are independently halo, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted C_{1-6} alkyl, cyano or $C(O)O_{0-1}R^8$ wherein R^8 is C_{1-6} alkyl; and

R^1, R^2, R^3, R^4, E, Z^1, Z^2 and Z^3 are as defined in claim 1.

3. The compound of claim 2, wherein Z^3 is NR^6 or $N(R^6)^+$-O^-; and Z^1 and Z^2 are CH_2.

4. The compound of claim 3, wherein R^6 is H, C_{1-6} alkyl optionally substituted with halo and/or hydroxyl groups; $-(CR_2)_p-OR^7$, $-(CR_2)_p-CH(OH)C_tF_{2t+1}$ wherein t is 1-3, $(CR_2)_p-CN$; $(CR_2)_p-NR(R^7)$, $-(CR_2)_p-C(O)OR^7$, $C(O)(CR_2)_qOR^8$, $-C(O)O-(CR_2)_p-NRR^7$, L-Y, -L-C(O)R^7, -L-C(O)-NRR^7, -L-C(O)-NR-$(CR_2)_p$-NRR^7, -L-C(O)-$(CR_2)_q$-NR-C(O)-R^8, -L-$S(O)_2R^8$, -L-$S(O)_2$-$(CR_2)_q$-NRR^7, or a radical selected from formula (a), (b), (c) or (d):



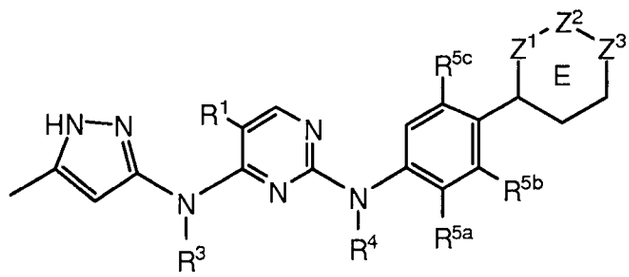
(a) (b) (c) (d)

R^{10} is O, S, NR^{17} wherein R^{17} is H, C_{1-6} alkyl, SO_2R^{8a} or CO_2R^{8a} and R^{8a} is C_{1-6} alkyl; and

R^7, R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R, L, Y, p and q are as defined in claim 1.

5. The compound of any one of claims 1-4, wherein R^2 is pyrazolyl, isoxazolyl, pyridine-2-onyl or azepan-2-onyl, each of which is substituted with C_{1-6} alkyl, C_{1-6} haloalkyl or C_{3-7} cycloalkyl.

6. The compound of claim 1, wherein said compound is of Formula (3):



(3)

or a tautomer thereof;

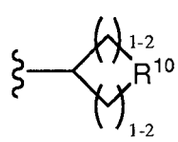
wherein R^{5b} is H; and R^{5a} and R^{5c} are independently halo, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted C_{1-6} alkyl, cyano or $C(O)O_{0-1}R^8$ wherein R^8 is C_{1-6} alkyl;

Z^1 and Z^2 are CH^2;

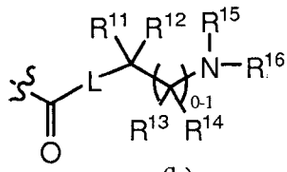
Z^3 is NR^6 or $N(R^6)^+$-O^-;

R^6 is H, C_{1-6} alkyl optionally substituted with halo and/or hydroxyl groups; $-(CR_2)_p$-OR^7, $-(CR_2)_p$-$CH(OH)C_tF_{2t+1}$ wherein t is 1-3, $(CR_2)_p$-CN; $(CR_2)_p$-$NR(R^7)$, $-(CR_2)_p$–$C(O)OR^7$, $C(O)(CR_2)_qOR^8$, $-C(O)O-(CR_2)_p$-NRR^7, L-Y, -L-$C(O)R^7$, -L–C(O)-NRR^7, -L–C(O)-NR-$(CR_2)_p$-NRR^7, -L–C(O)-$(CR_2)_q$-NR-C(O)-R^8, -L-$S(O)_2R^8$,

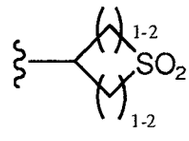
-L-$S(O)_2$-$(CR_2)_q$-NRR^7, or a radical selected from formula (a), (b), (c) or (d):



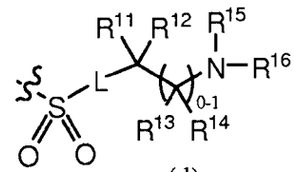
(a)



(b)



(c)



(d)

R^{10} is O, S, NR^{17} wherein R^{17} is H, C_{1-6} alkyl, SO_2R^{8a} or CO_2R^{8a} and R^{8a} is C_{1-6} alkyl; and

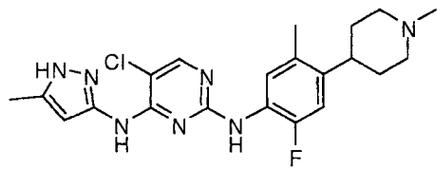
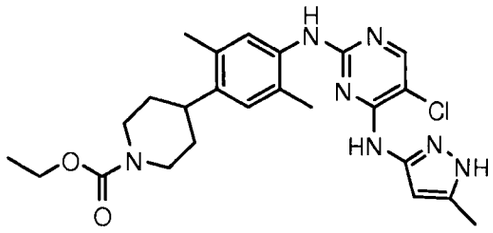
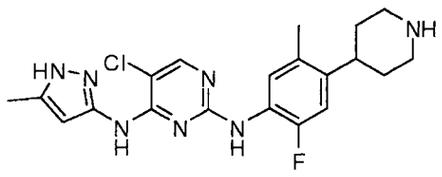
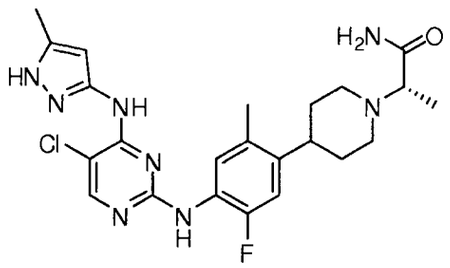
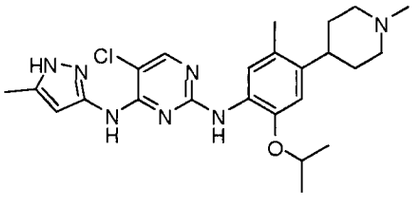
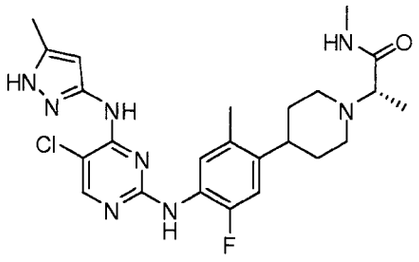
R^1, R^3, R^4, R^7, R^8, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R, L, Y, p, q and E are as defined in claim 1.

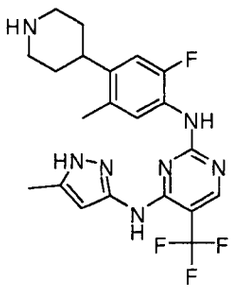
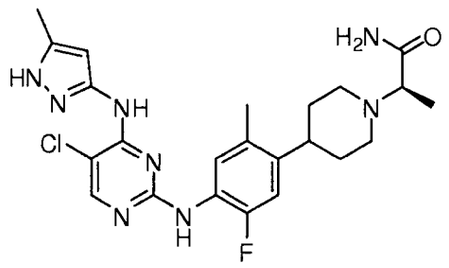
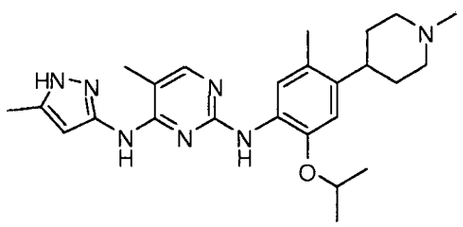
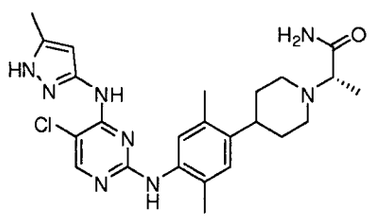
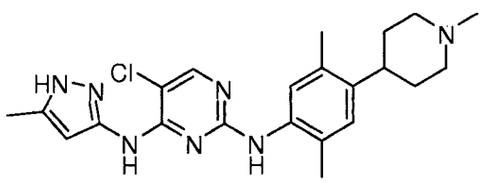
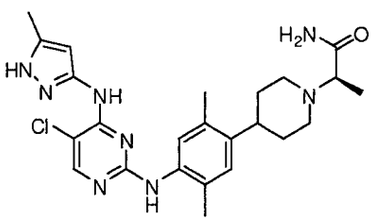
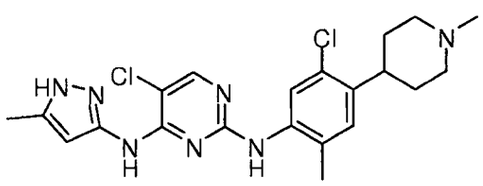
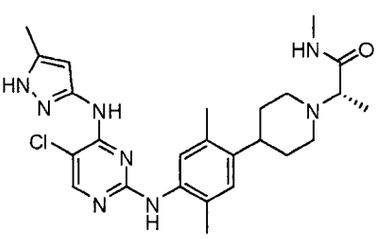
7. The compound of claim 6, wherein R^{5a} is halo and R^{5c} is C_{1-6} alkyl.

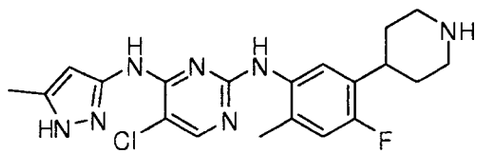
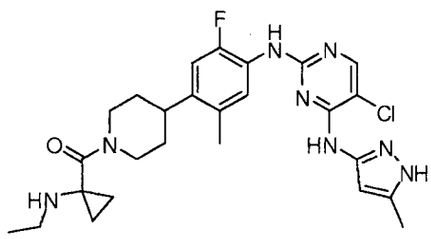
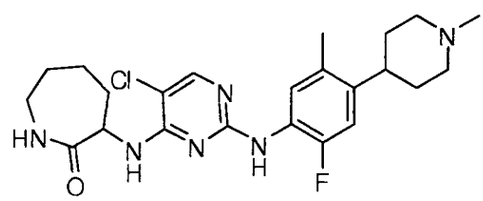
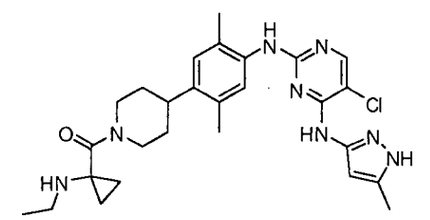
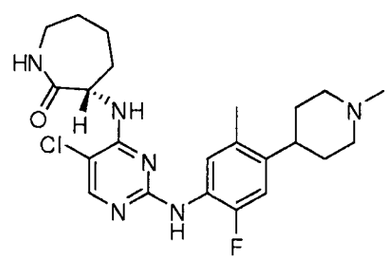
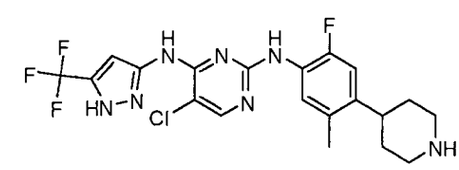
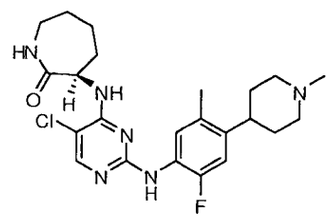
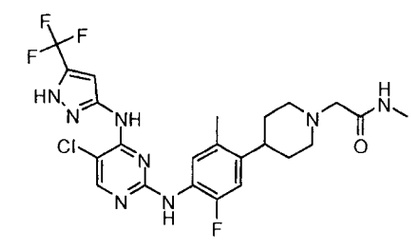
8. The compound of claim 6, wherein R^6 is C_{1-6} alkyl or a a radical of formula (a) or (c); and R^{10} is O.

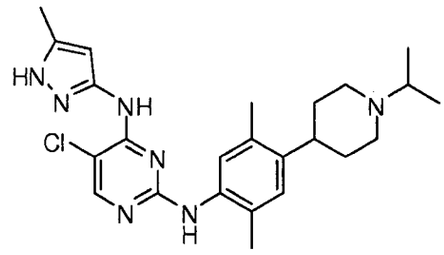
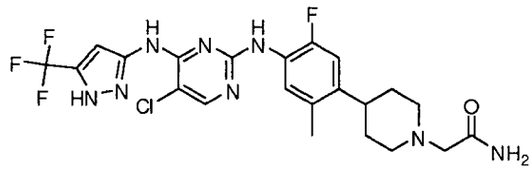
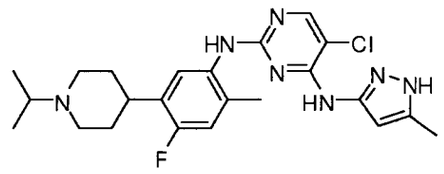
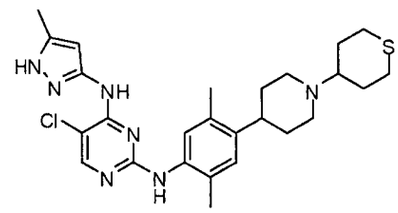
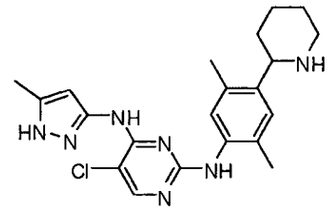
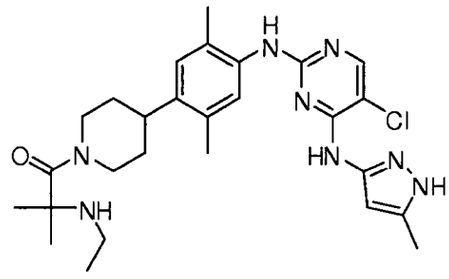
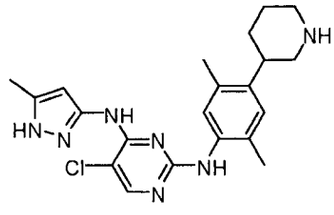
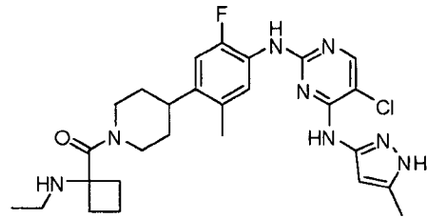
9. The compound of any one of claims 1-8, wherein R^1 is halo.

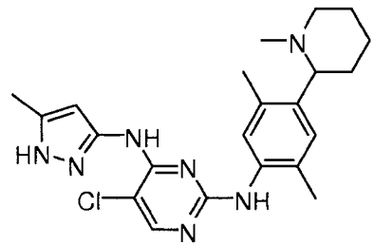
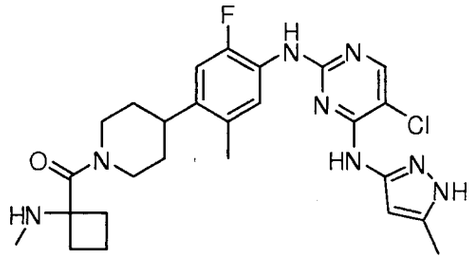
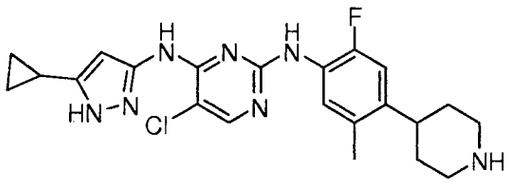
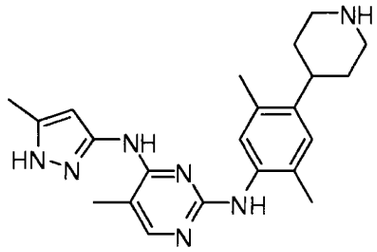
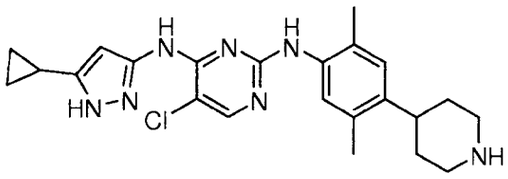
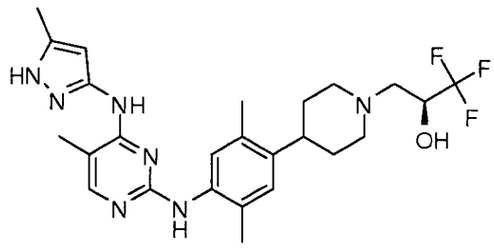
10. The compound of claim 1, wherein said compound is selected from the group

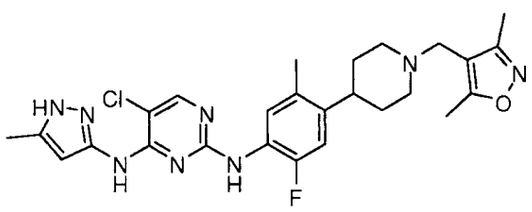
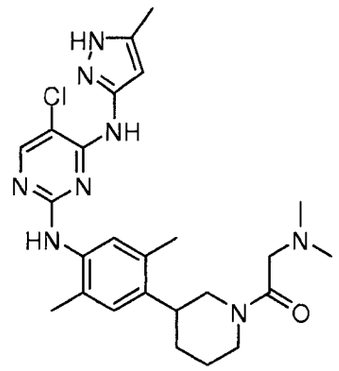
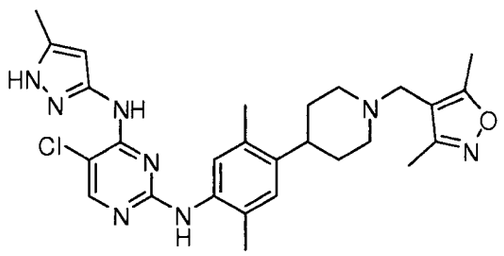
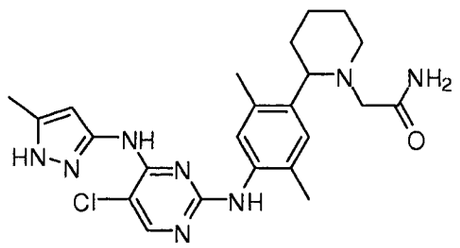
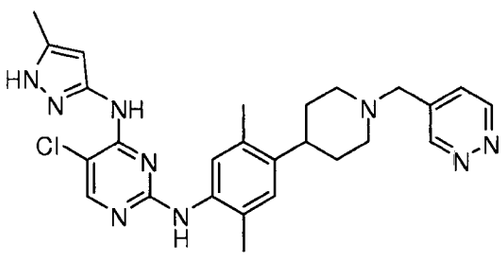
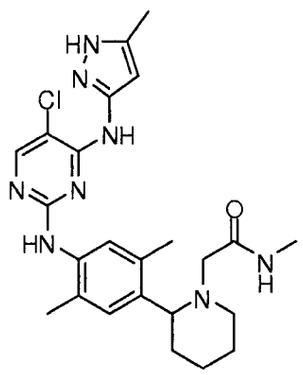
 5-chloro-N2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 ethyl 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidine-1-carboxylate
 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 (S)-2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)propanamide
 5-chloro-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 (S)-2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-N-methylpropanamide

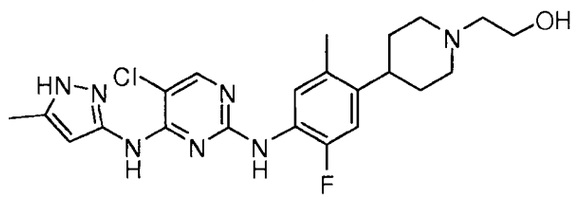
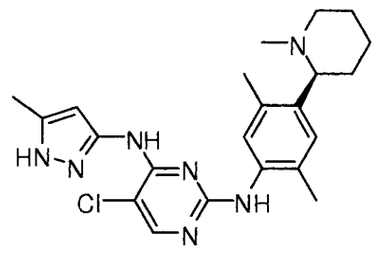
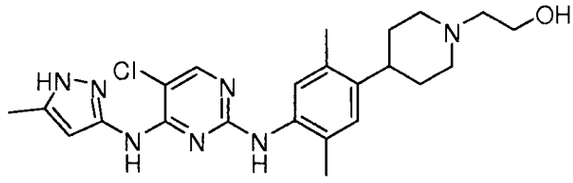
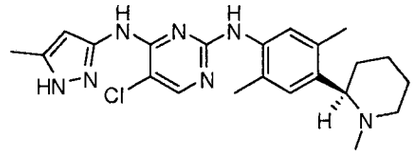
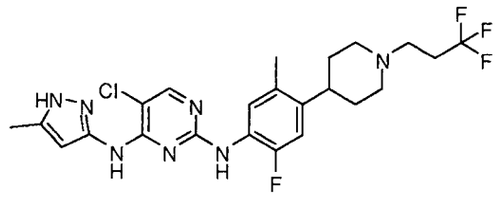
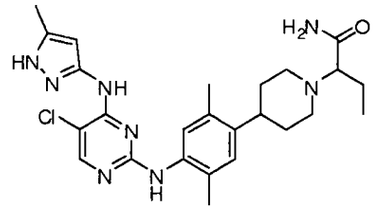
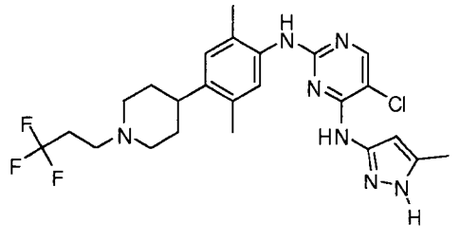
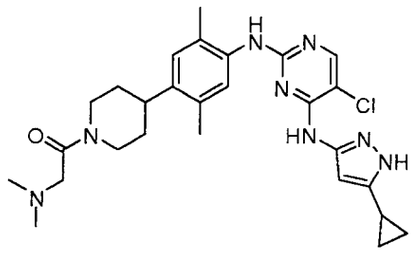
 N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine	 (R)-2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)propanamide
 N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-5-methyl-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 (S)-2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)propanamide
 5-chloro-N2-(2,5-dimethyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 (R)-2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)propanamide
 5-chloro-N2-(5-chloro-2-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 (S)-2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylpropanamide

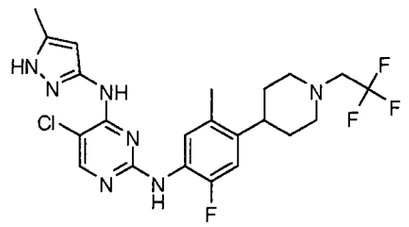
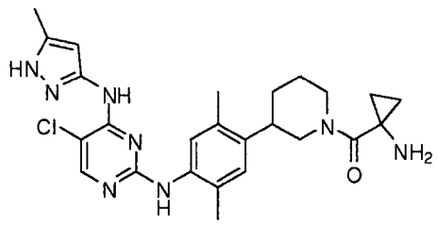
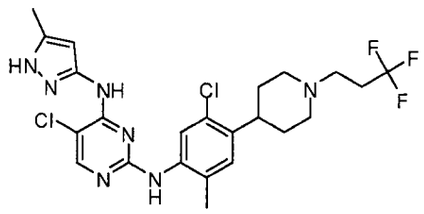
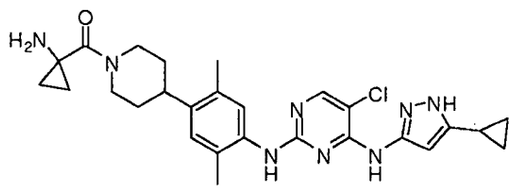
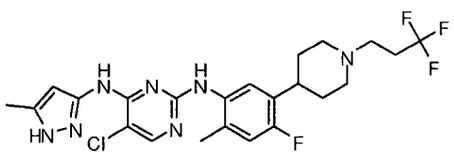
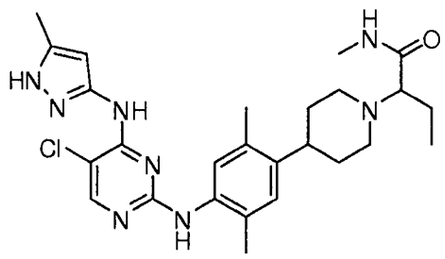
 5-chloro-N2-(4-fluoro-2-methyl-5-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-(ethylamino)cyclopropyl)methanone
 3-(5-chloro-2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)azepan-2-one	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)(1-(ethylamino)cyclopropyl)methanone
 (S)-3-(5-chloro-2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)azepan-2-one	 5-chloro-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(5-(trifluoromethyl)-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 (R)-3-(5-chloro-2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)azepan-2-one	 2-(4-(4-(5-chloro-4-(5-(trifluoromethyl)-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-N-methylacetamide

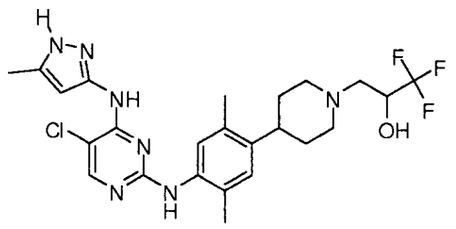
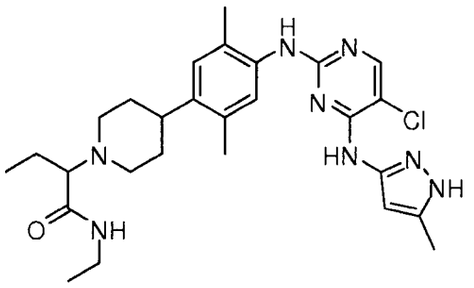
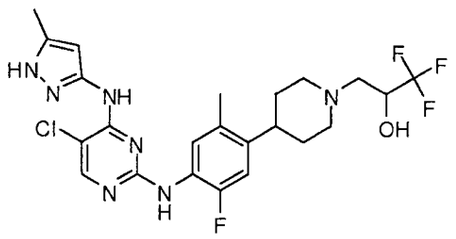
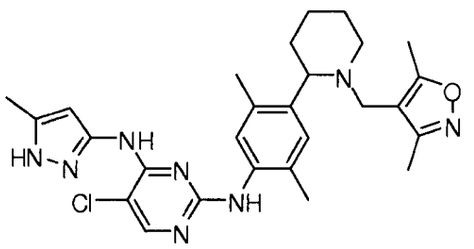
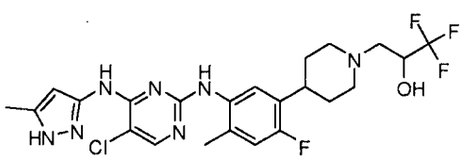
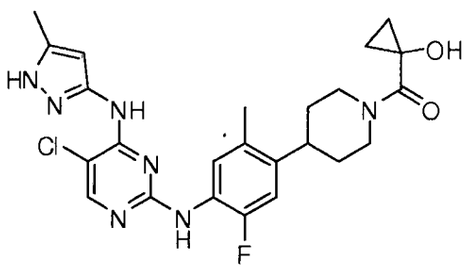
 5-chloro-N2-(4-(1-isopropylpiperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 2-(4-(4-(5-chloro-4-(5-(trifluoromethyl)-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)acetamide
 5-chloro-N2-(4-fluoro-5-(1-isopropylpiperidin-4-yl)-2-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 5-chloro-N2-(2,5-dimethyl-4-(1-(tetrahydro-2H-thiopyran-4-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 5-chloro-N2-(2,5-dimethyl-4-(piperidin-2-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(ethylamino)-2-methylpropan-1-one
 5-chloro-N2-(2,5-dimethyl-4-(piperidin-3-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-(ethylamino)cyclobutyl)methanone

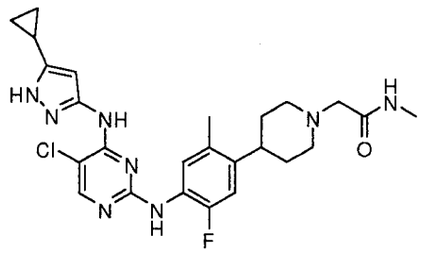
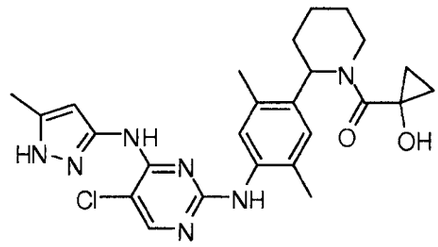
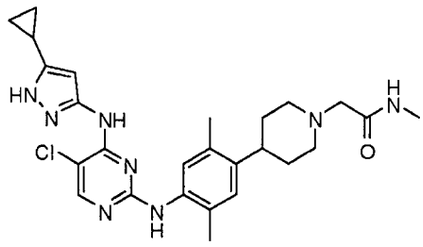
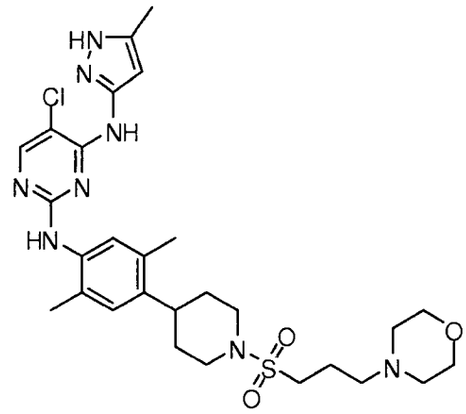
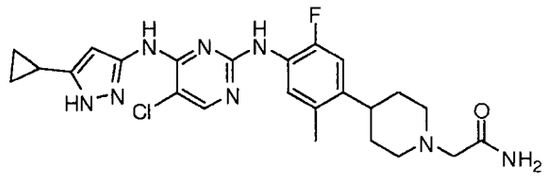
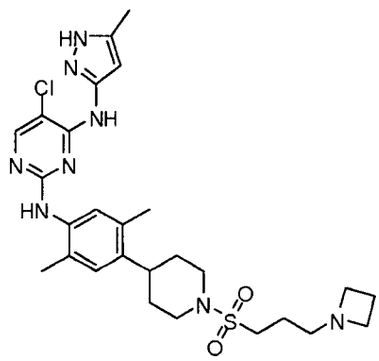
 5-chloro-N2-(2,5-dimethyl-4-(1-methylpiperidin-2-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-(methylamino)cyclobutyl)methanone
 5-chloro-N4-(5-cyclopropyl-1H-pyrazol-3-yl)-N2-(2-fluoro-5-methyl-4-(piperidin-4-yl)phenyl)pyrimidine-2,4-diamine	 N2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-5-methyl-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 5-chloro-N4-(5-cyclopropyl-1H-pyrazol-3-yl)-N2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)pyrimidine-2,4-diamine	 (S)-3-(4-(2,5-dimethyl-4-(5-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)phenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol

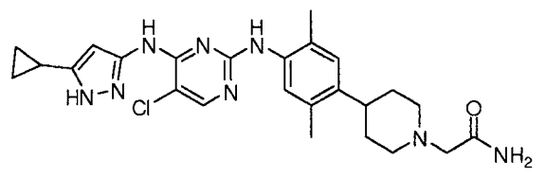
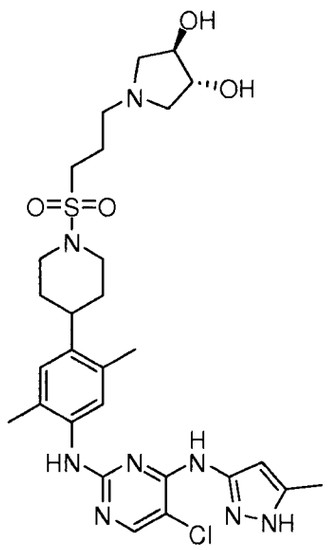
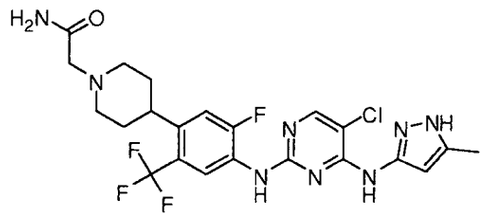
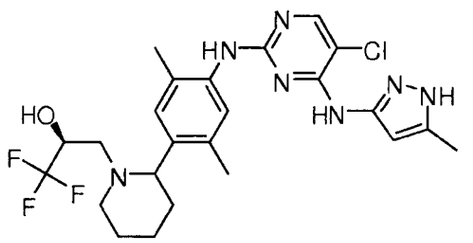
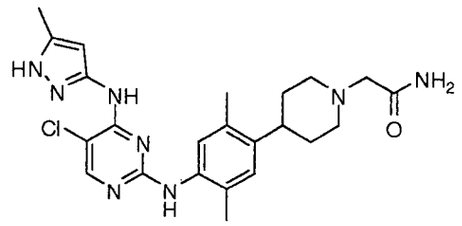
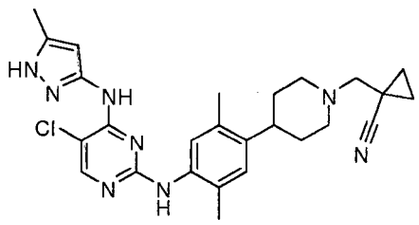
 5-Chloro-N2-(4-(1-((3,5-dimethylisoxazol-4-yl)methyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 1-(3-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone
 5-chloro-N2-(4-(1-((3,5-dimethylisoxazol-4-yl)methyl)piperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 2-(2-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)acetamide
 5-chloro-N2-(2,5-dimethyl-4-(1-(pyridazin-4-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 2-(2-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide

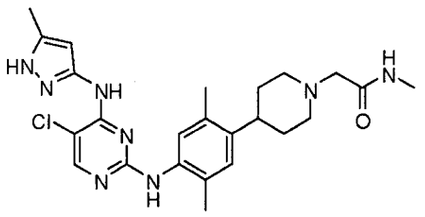
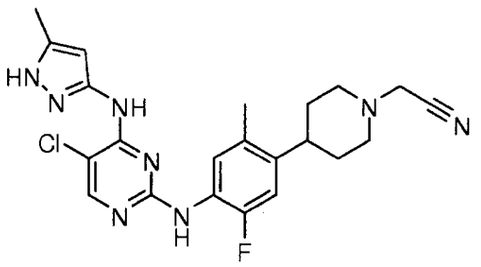
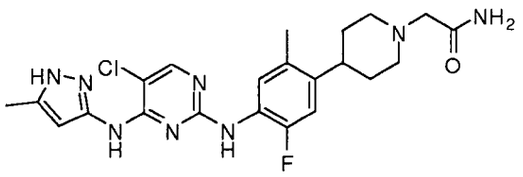
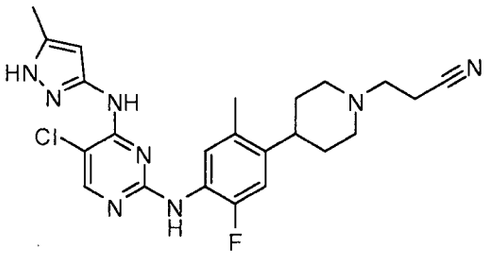
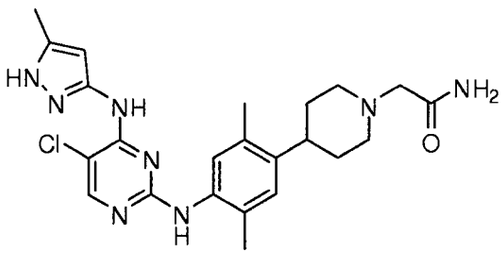
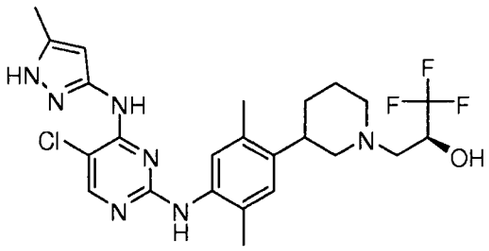
 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)ethanol	 (S)-5-chloro-N2-(2,5-dimethyl-4-(1-methylpiperidin-2-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)ethanol	 (R)-5-chloro-N2-(2,5-dimethyl-4-(1-methylpiperidin-2-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 5-chloro-N^2-(2-fluoro-5-methyl-4-(1-(3,3,3-trifluoropropyl)piperidin-4-yl)phenyl)- N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)butanamide
 5-chloro-N2-(2,5-dimethyl-4-(1-(3,3,3-trifluoropropyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 1-(4-(4-(5-chloro-4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone

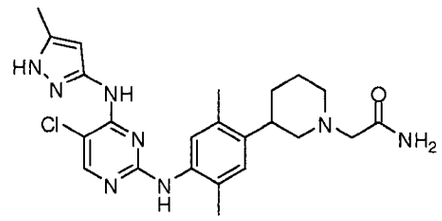
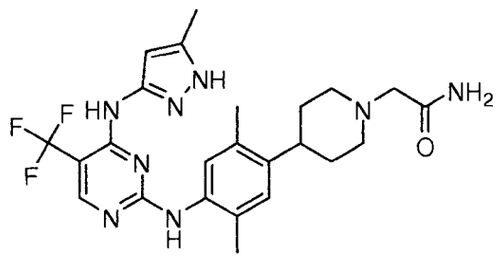
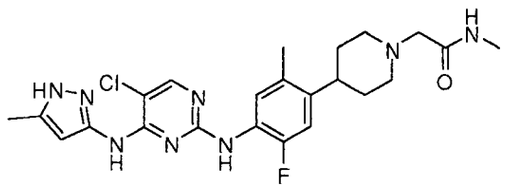
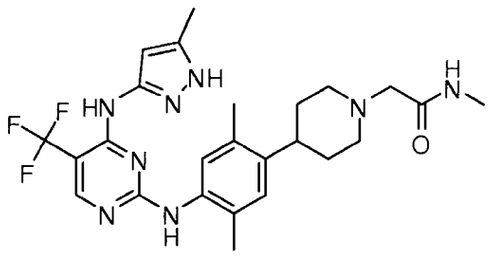
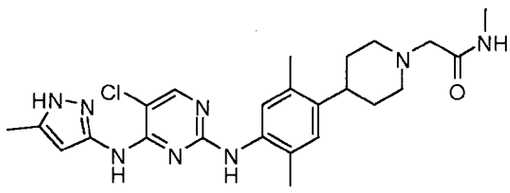
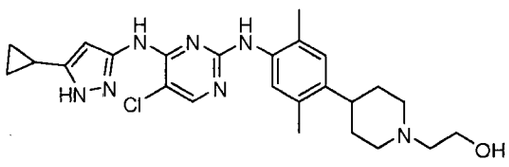
 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 (1-aminocyclopropyl)(3-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)methanone
 5-chloro-N2-(5-chloro-2-methyl-4-(1-(3,3,3-trifluoropropyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 (1-aminocyclopropyl)(4-(4-(5-chloro-4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)methanone
 5-chloro-N2-(4-fluoro-2-methyl-5-(1-(3,3,3-trifluoropropyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylbutanamide

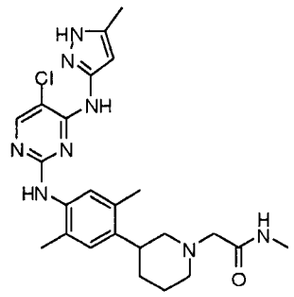
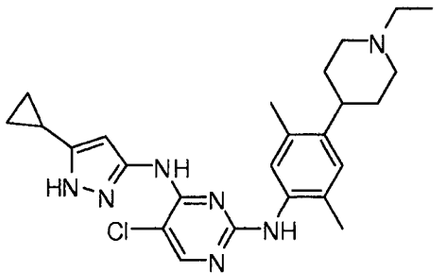
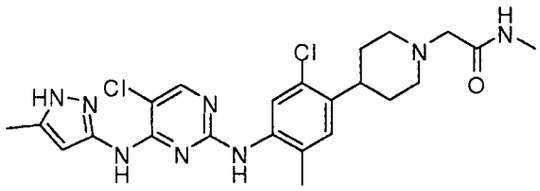
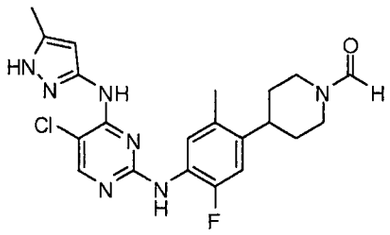
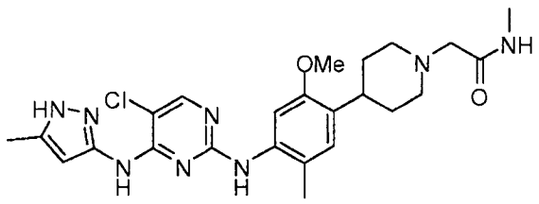
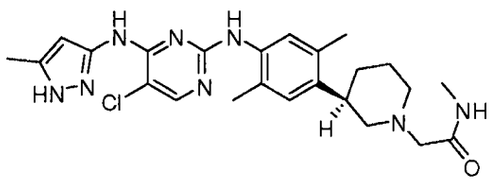
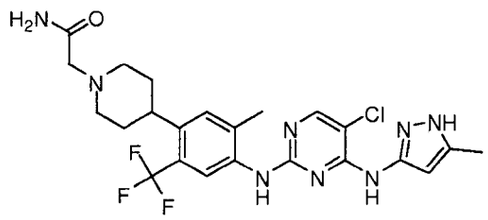
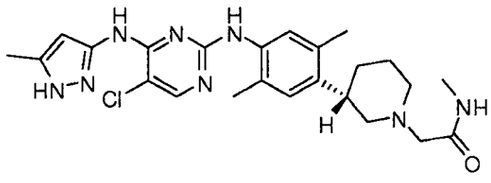
 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl) piperidin-1-yl)-1,1,1-trifluoropropan-2-ol	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-ethylbutanamide
 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino) pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl) piperidin-1-yl)-1,1,1-trifluoropropan-2-ol	 5-chloro-N2-(4-(1-((3,5-dimethylisoxazol-4-yl)methyl)piperidin-2-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 3-(4-(5-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2-fluoro-4-methylphenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-hydroxycyclopropyl)methanone

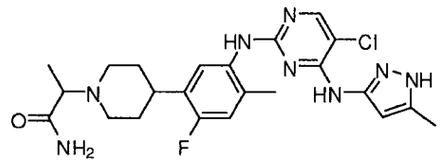
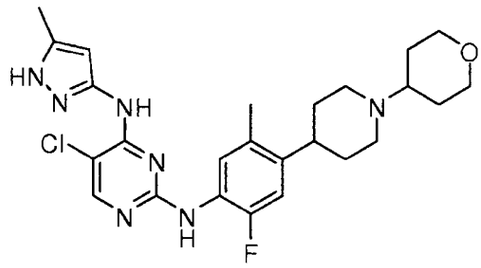
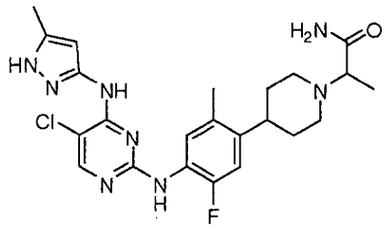
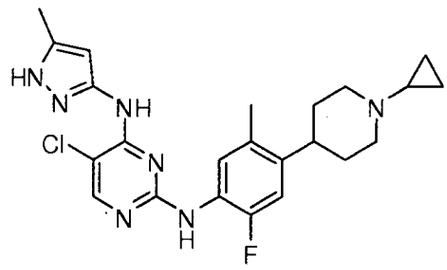
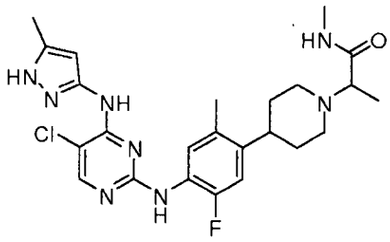
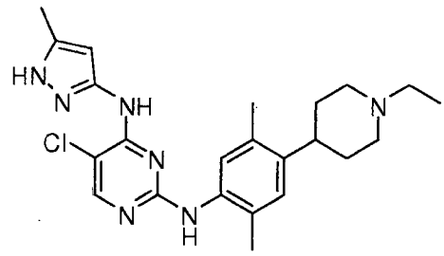
 2-(4-(4-(5-chloro-4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-N-methylacetamide	 (2-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)(1-hydroxycyclopropyl)methanone
 2-(4-(4-(5-chloro-4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide	 5-chloro-N2-(2,5-dimethyl-4-(1-(3-morpholinopropylsulfonyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 2-(4-(4-(5-chloro-4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)acetamide	 N2-(4-(1-(3-(azetidin-1-yl)propylsulfonyl)piperidin-4-yl)-2,5-dimethylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

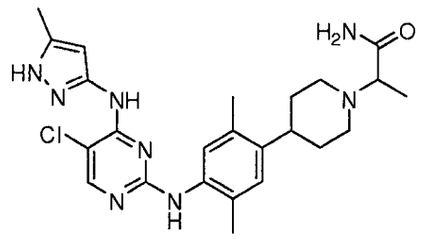
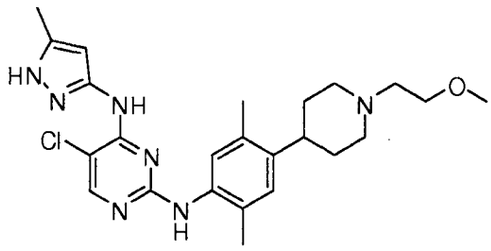
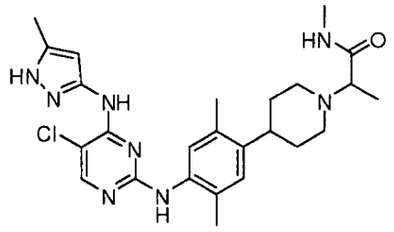
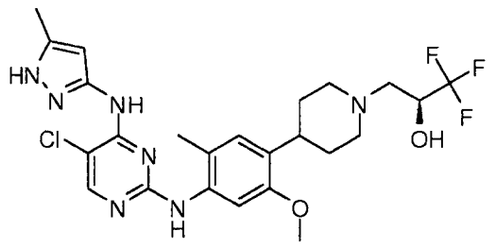
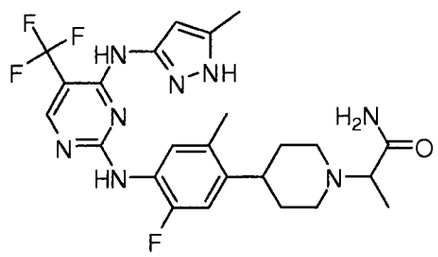
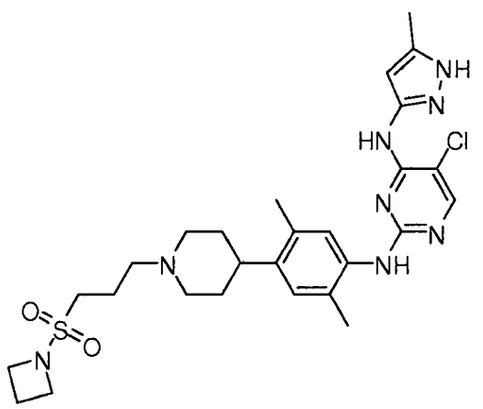
 2-(4-(4-(5-chloro-4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)acetamide	 (3R,4R)-1-(3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-ylsulfonyl)propyl)pyrrolidine-3,4-diol
 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-(trifluoromethyl)phenyl)piperidin-1-yl)acetamide	 (2S)-3-(2-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol
 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)acetamide	 1-((4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)methyl)cyclopropanecarbonitrile

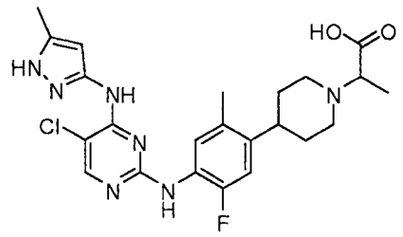
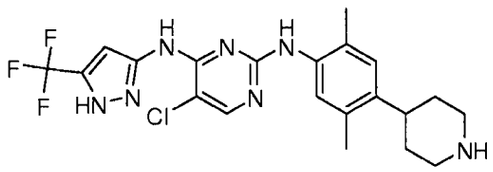
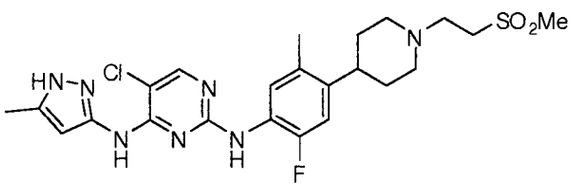
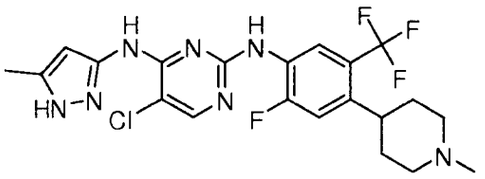
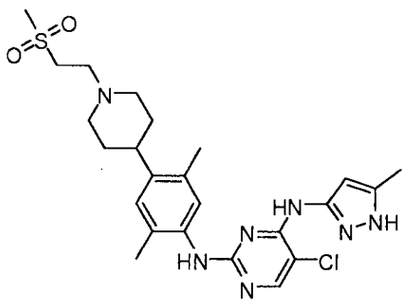
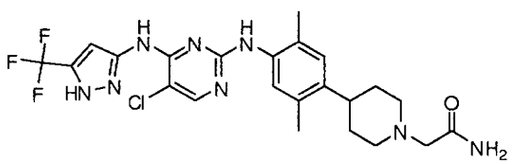
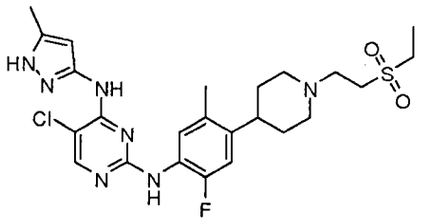
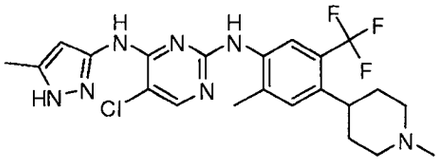
 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)acetonitrile
 2-(4-(4-(5-Chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)acetamide	 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)propanenitrile
 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)acetamide	 (2S)-3-(3-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol

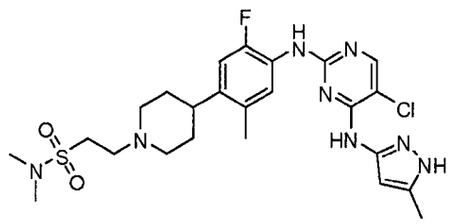
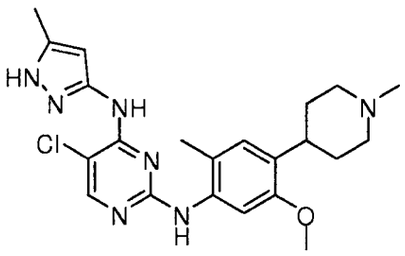
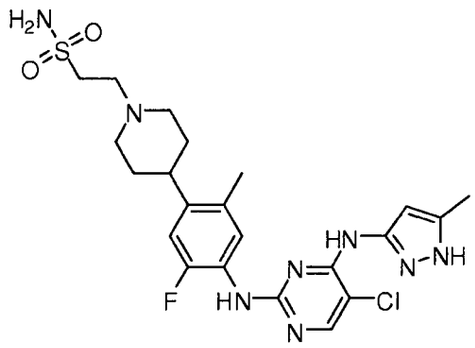
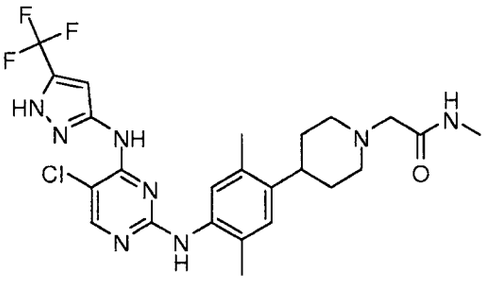
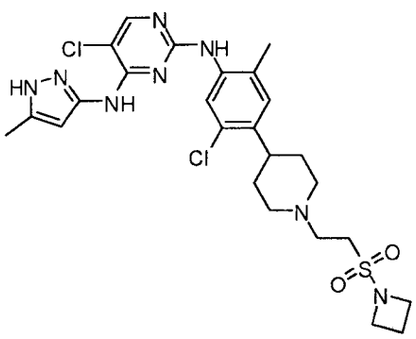
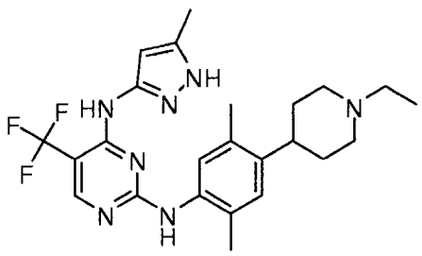
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 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-N-methylacetamide	 2-(4-(2,5-dimethyl-4-(4-(5-methyl-1H-pyrazol-3-ylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)piperidin-1-yl)-N-methylacetamide
 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide	 2-(4-(4-(5-chloro-4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)ethanol

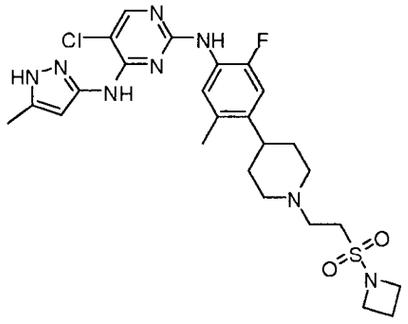
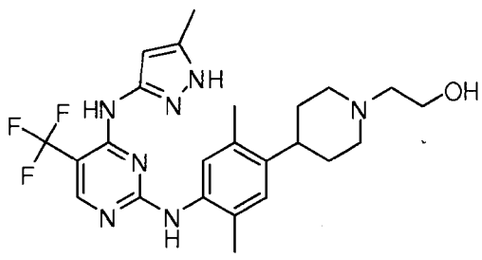
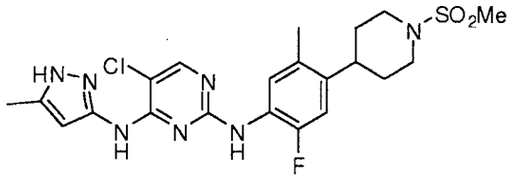
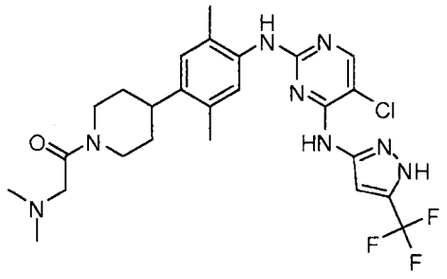
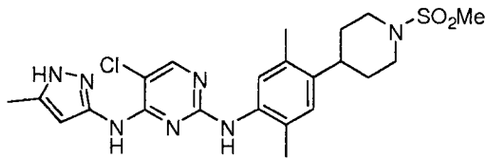
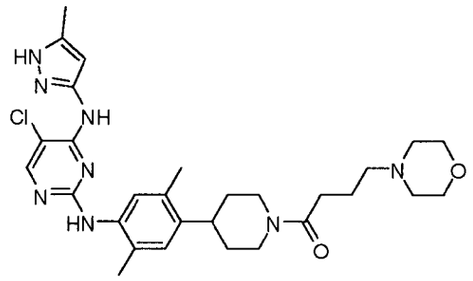
 2-(3-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide	 5-chloro-N4-(5-cyclopropyl-1H-pyrazol-3-yl)-N2-(4-(1-ethylpiperidin-4-yl)-2,5-dimethylphenyl)pyrimidine-2,4-diamine
 2-(4-(2-chloro-4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-methylphenyl)piperidin-1-yl)-N-methylacetamide	 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidine-1-carbaldehyde
 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2-methoxy-5-methylphenyl)piperidin-1-yl)-N-methylacetamide	 (R)-2-(3-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide
 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-methyl-2-(trifluoromethyl)phenyl)piperidin-1-yl)acetamide	 (S)-2-(3-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide

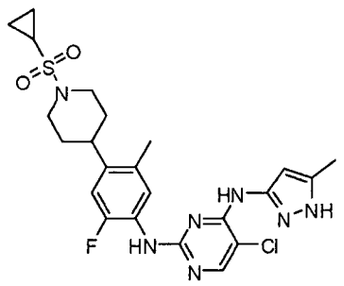
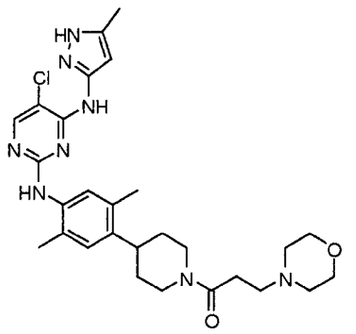
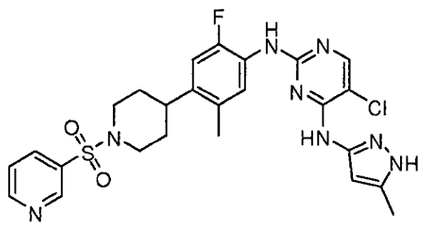
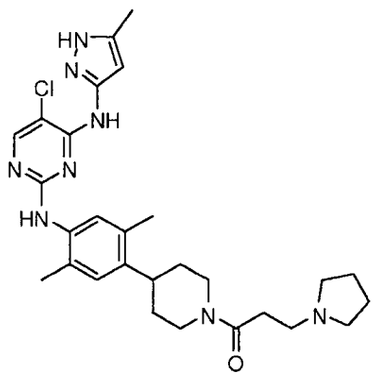
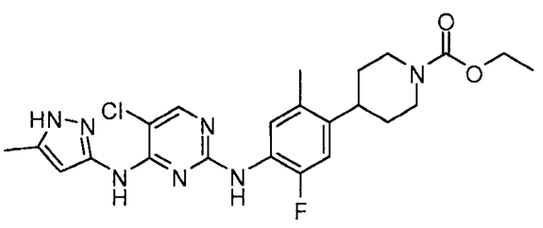
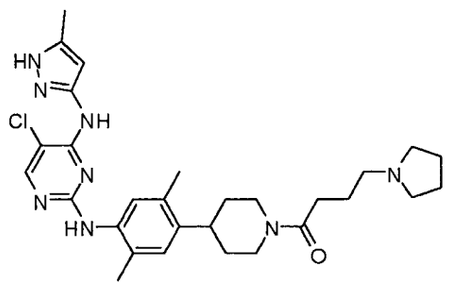
 2-(4-(5-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2-fluoro-4-methylphenyl)piperidin-1-yl)propanamide	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)propanamide	 5-chloro-N2-(4-(1-cyclopropylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-N-methylpropanamide	 5-chloro-N2-(4-(1-ethylpiperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

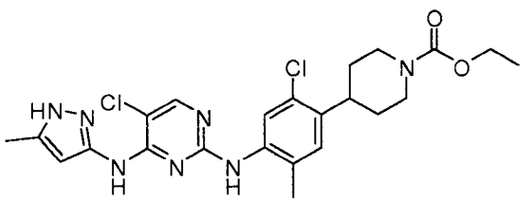
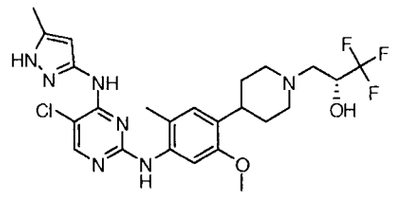
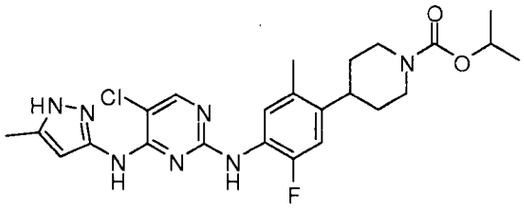
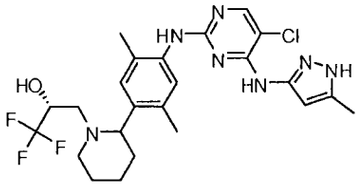
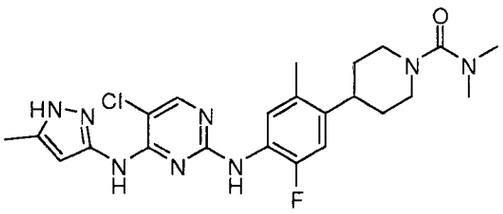
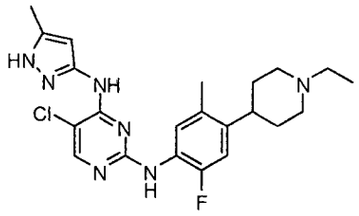
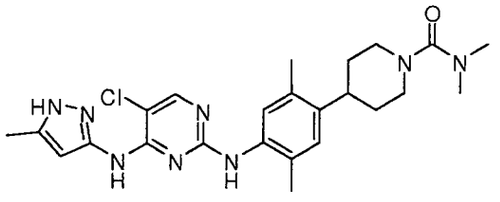
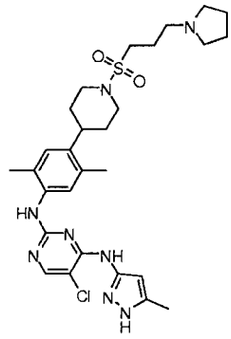
 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)propanamide	 5-chloro-N2-(4-(1-(2-methoxyethyl)piperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylpropanamide	 (S)-3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2-methoxy-5-methylphenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol
 2-(4-(5-fluoro-2-methyl-4-(4-(5-methyl-1H-pyrazol-3-ylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)piperidin-1-yl)propanamide	 N2-(4-(1-(3-(azetidin-1-ylsulfonyl)propyl)piperidin-4-yl)-2,5-dimethylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

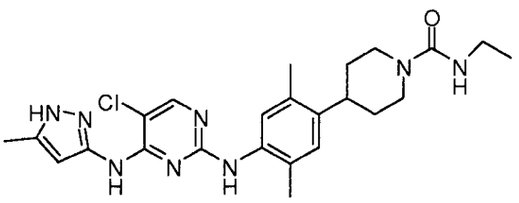
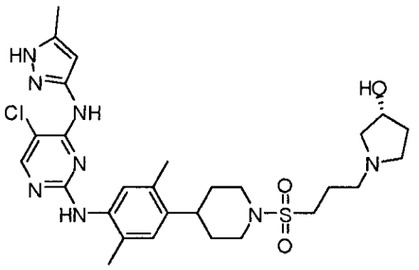
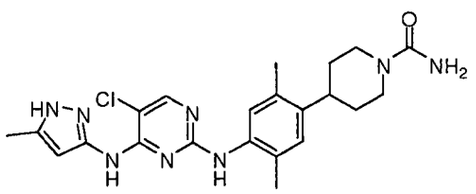
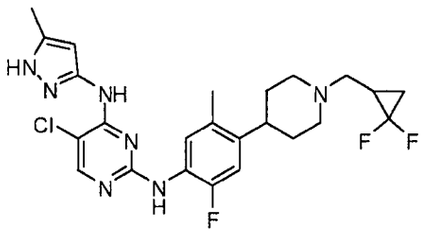
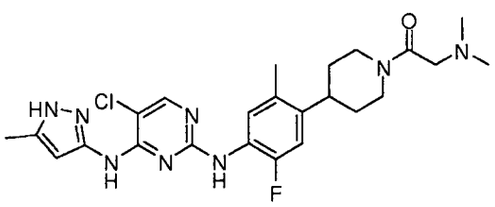
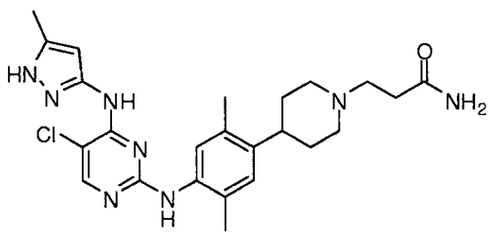
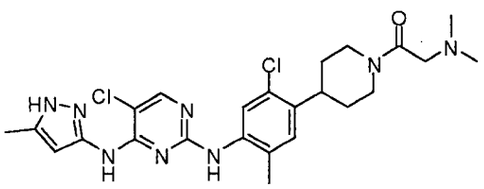
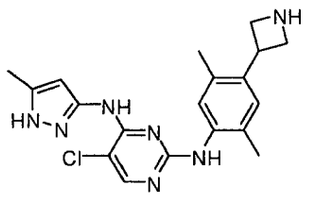
 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)propanoic acid	 5-chloro-N2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-N4-(5-(trifluoromethyl)-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 5-Chloro-N2-(2-fluoro-5-methyl-4-(1-(2-(methylsulfonyl)ethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 5-chloro-N2-(2-fluoro-4-(1-methylpiperidin-4-yl)-5-(trifluoromethyl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 5-chloro-N2-(2,5-dimethyl-4-(1-(2-(methylsulfonyl)ethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 2-(4-(4-(5-chloro-4-(5-(trifluoromethyl)-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)acetamide
 5-chloro-N2-(4-(1-(2-(ethylsulfonyl)ethyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)-N2-(2-methyl-4-(1-methylpiperidin-4-yl)-5-(trifluoromethyl)phenyl)pyrimidine-2,4-diamine

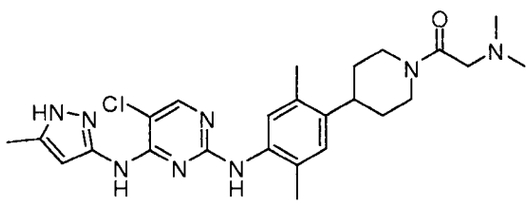
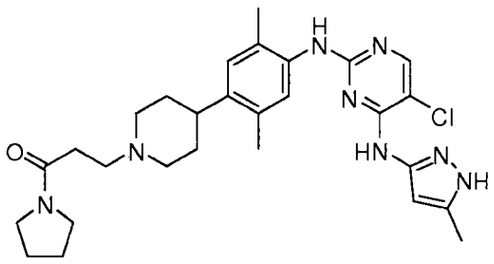
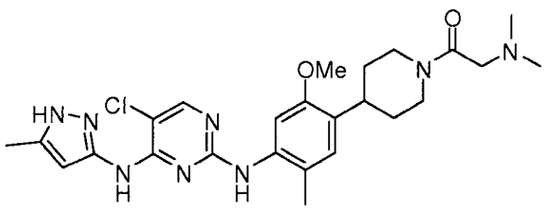
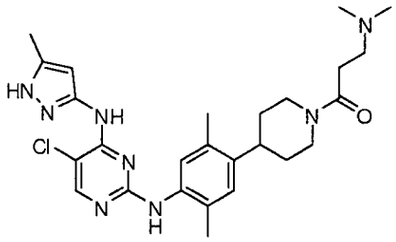
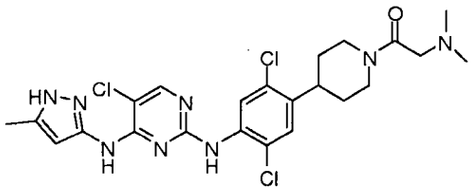
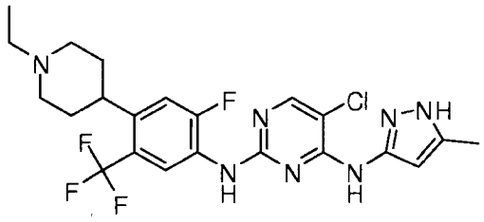
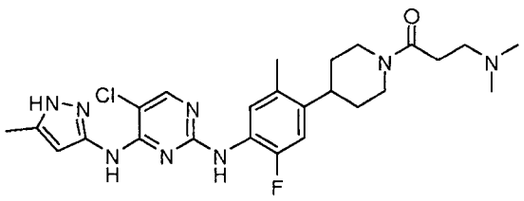
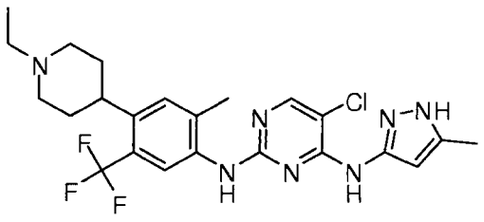
 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-N,N-dimethylethanesulfonamide	 5-chloro-N2-(5-methoxy-2-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)ethanesulfonamide	 2-(4-(4-(5-chloro-4-(5-(trifluoromethyl)-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-N-methylacetamide
 N2-(4-(1-(2-(azetidin-1-ylsulfonyl)ethyl)piperidin-4-yl)-5-chloro-2-methylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 N2-(4-(1-ethylpiperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine

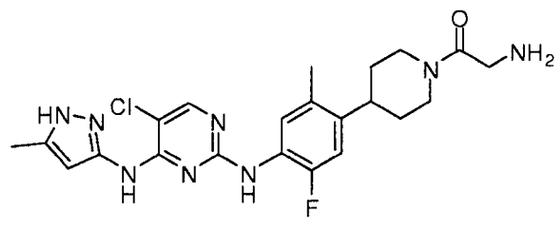
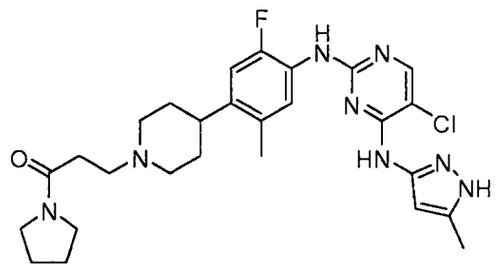
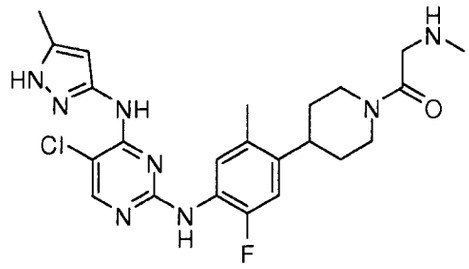
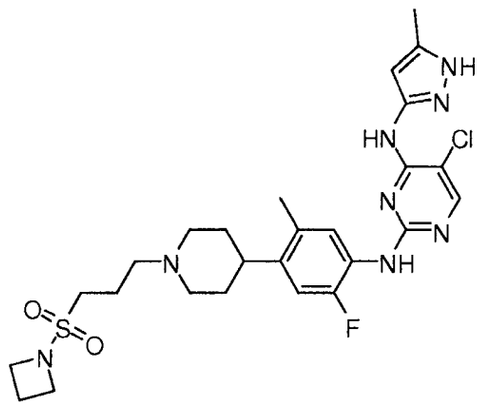
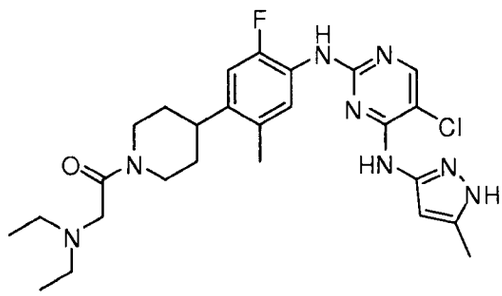
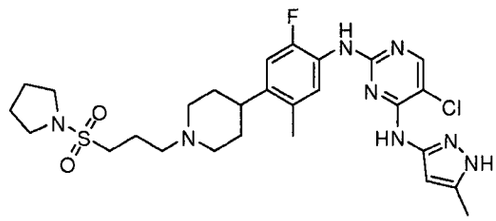
 N2-(4-(1-(2-(azetidin-1-ylsulfonyl)ethyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 2-(4-(2,5-dimethyl-4-(4-(5-methyl-1H-pyrazol-3-ylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)piperidin-1-yl)ethanol
 5-Chloro-N2-(2-fluoro-5-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 1-(4-(4-(5-chloro-4-(5-(trifluoromethyl)-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone
 5-chloro-N2-(2,5-dimethyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-4-morpholinobutan-1-one

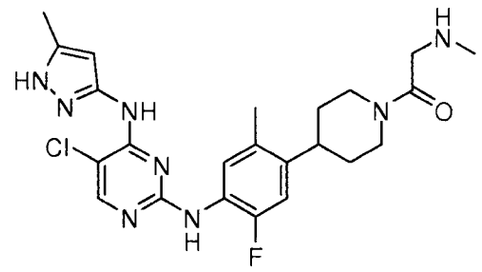
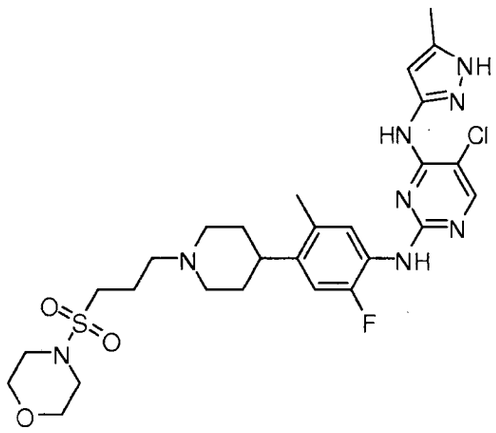
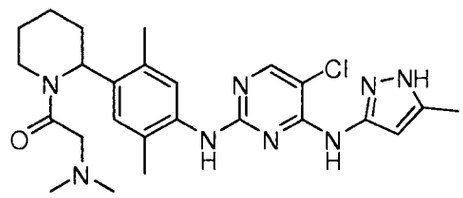
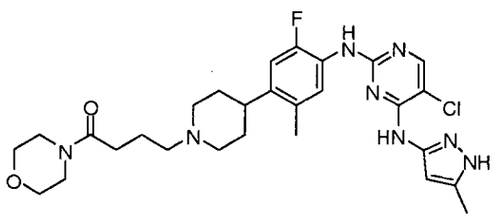
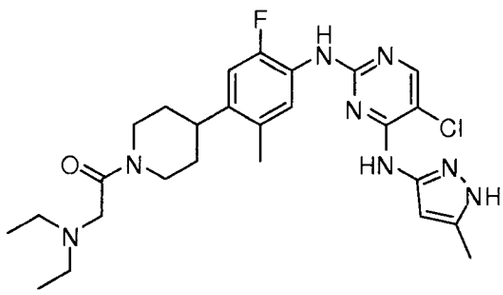
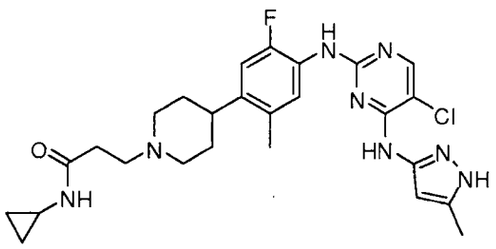
 5-chloro-N2-(4-(1-(cyclopropylsulfonyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-3-morpholinopropan-1-one
 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(pyridin-3-ylsulfonyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-3-(pyrrolidin-1-yl)propan-1-one
 Ethyl 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidine-1-carboxylate	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-4-(pyrrolidin-1-yl)butan-1-one

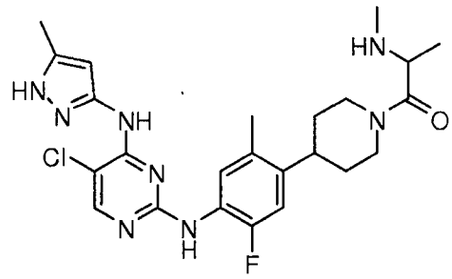
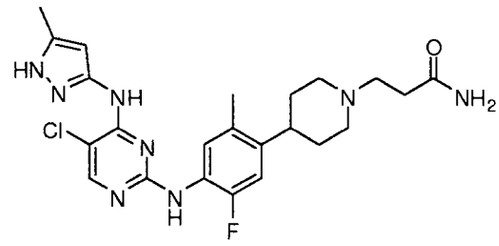
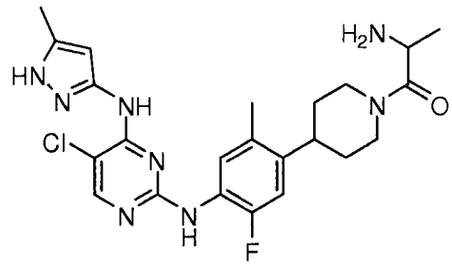
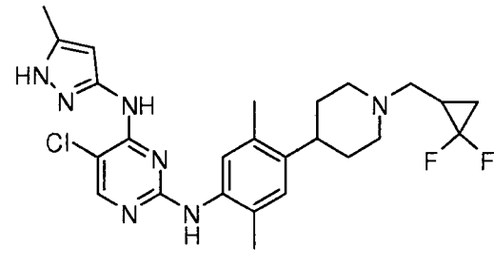
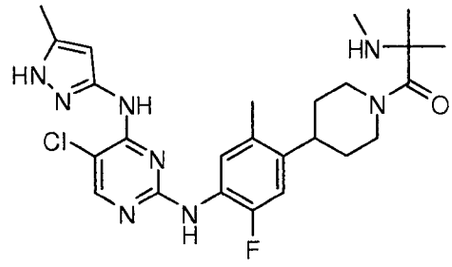
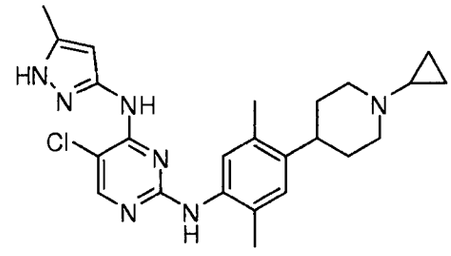
 ethyl 4-(2-chloro-4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-methylphenyl)piperidine-1-carboxylate	 (R)-3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2-methoxy-5-methylphenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol
 isopropyl 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidine-1-carboxylate	 (2R)-3-(2-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-1,1,1-trifluoropropan-2-ol
 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)-N,N-dimethylpiperidine-1-carboxamide	 5-chloro-N2-(4-(1-ethylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)-N,N-dimethylpiperidine-1-carboxamide	 5-chloro-N2-(2,5-dimethyl-4-(1-(3-(pyrrolidin-1-yl)propylsulfonyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

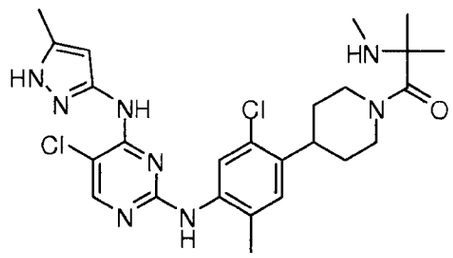
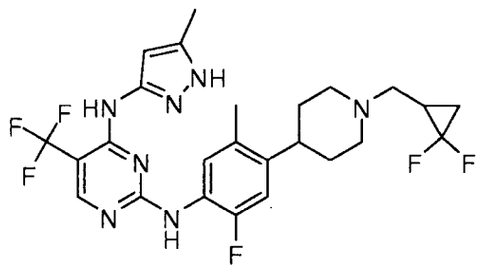
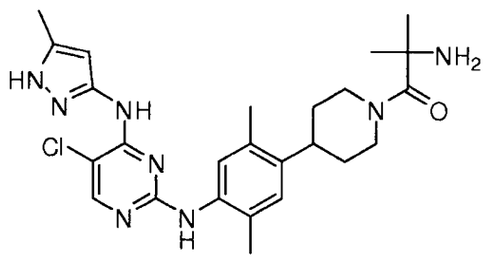
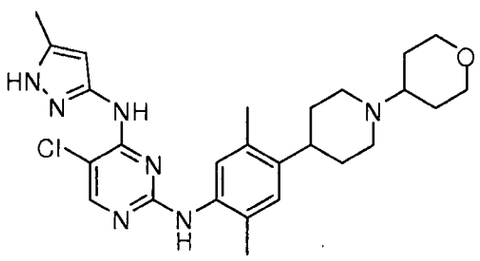
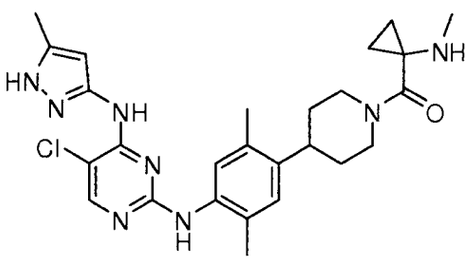
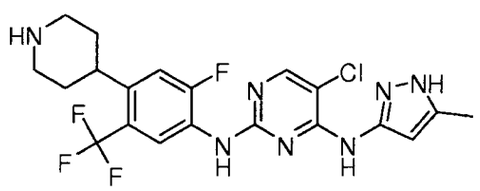
 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)-N-ethylpiperidine-1-carboxamide	 (R)-1-(3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-ylsulfonyl)propyl)pyrrolidin-3-ol
 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidine-1-carboxamide	 5-chloro-N2-(4-(1-((2,2-difluorocyclopropyl)methyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone	 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)propanamide
 1-(4-(2-chloro-4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-methylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone	 N2-(4-(azetidin-3-yl)-2,5-dimethylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

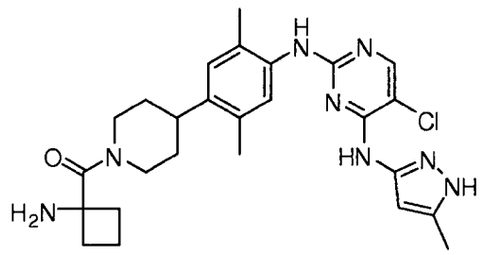
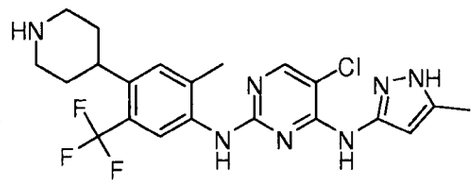
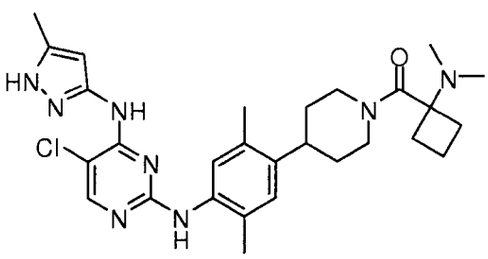
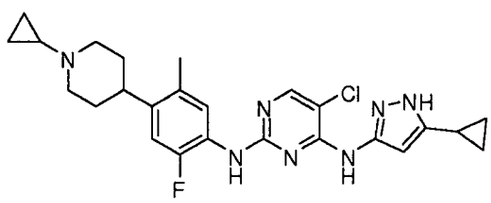
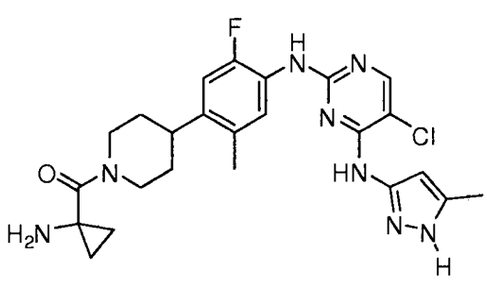
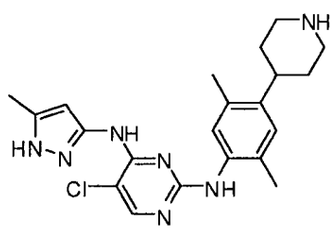
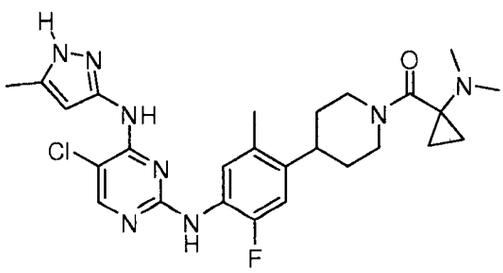
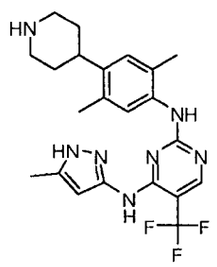
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone	 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-1-(pyrrolidin-1-yl)propan-1-one
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2-methoxy-5-methylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone	 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-3-(dimethylamino)propan-1-one
 1-(4-(2,5-dichloro-4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)phenyl)piperidin-1-yl)-2-(dimethylamino)ethanone	 5-chloro-N2-(4-(1-ethylpiperidin-4-yl)-2-fluoro-5-(trifluoromethyl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-3-(dimethylamino)propan-1-one	 5-chloro-N2-(4-(1-ethylpiperidin-4-yl)-2-methyl-5-(trifluoromethyl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

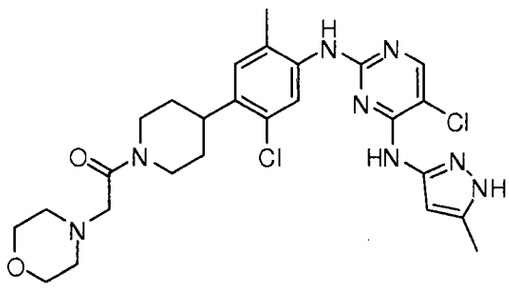
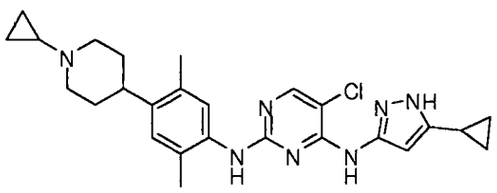
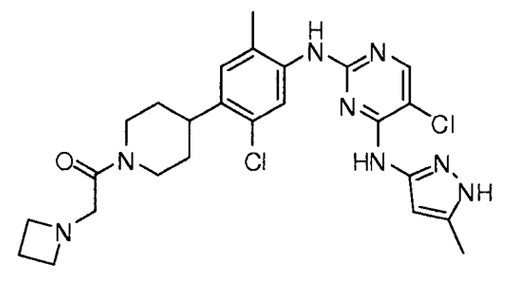
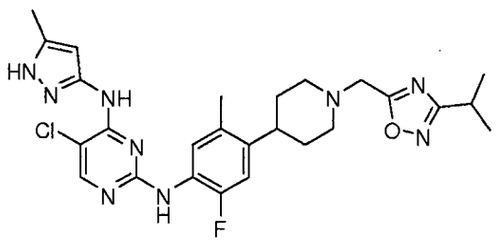
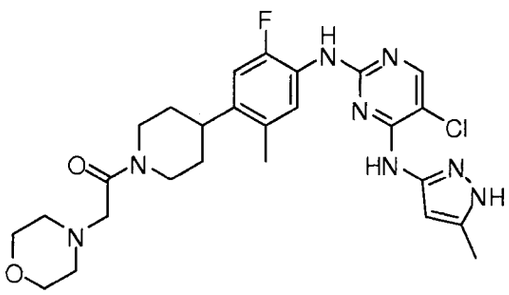
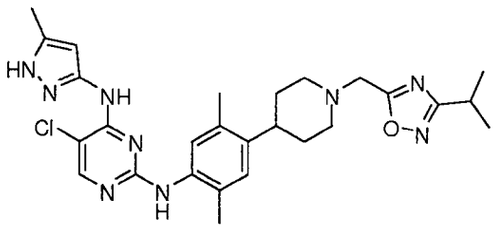
 2-amino-1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)ethanone	 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-1-(pyrrolidin-1-yl)propan-1-one
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(methylamino)ethanone	 N2-(4-(1-(3-(azetidin-1-ylsulfonyl)propyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(diethylamino)ethanone	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(3-(pyrrolidin-1-ylsulfonyl)propyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

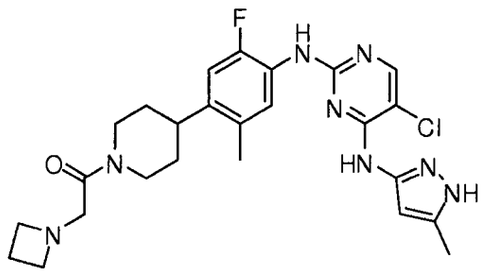
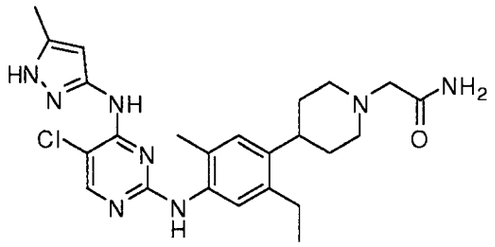
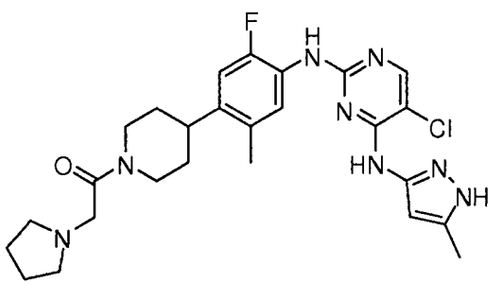
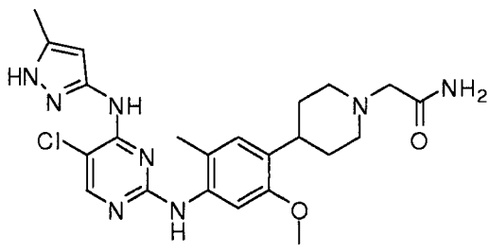
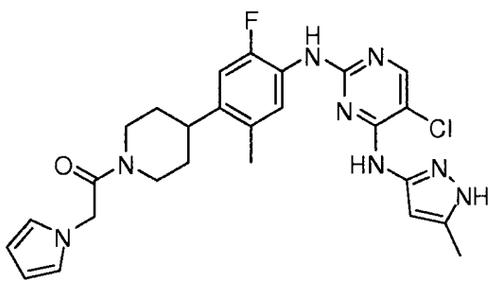
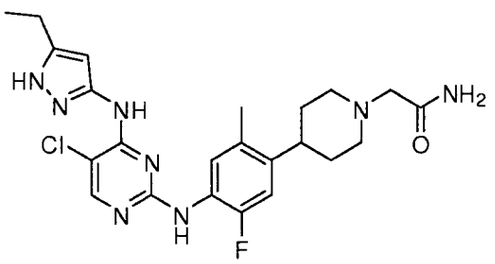
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(methylamino)ethanone	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(3-(morpholinosulfonyl)propyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 1-(2-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(dimethylamino)ethanone	 4-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-1-morpholinobutan-1-one
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(diethylamino)ethanone	 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-N-cyclopropylpropanamide

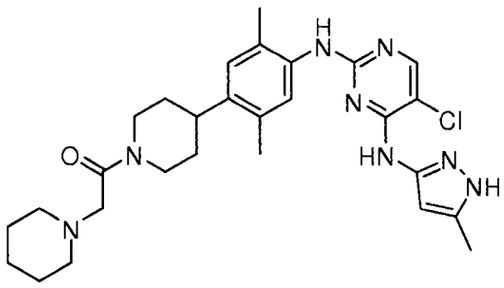
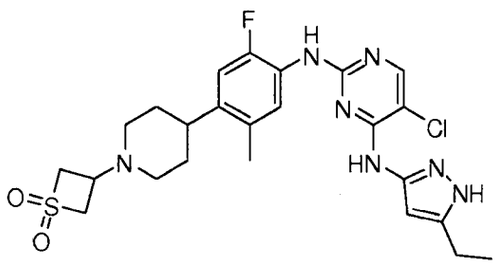
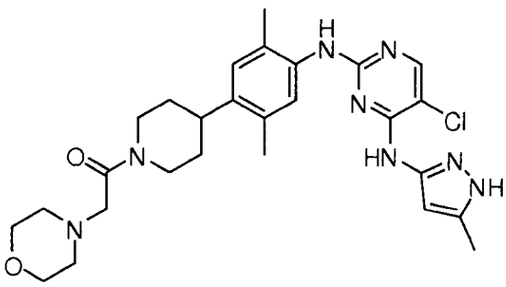
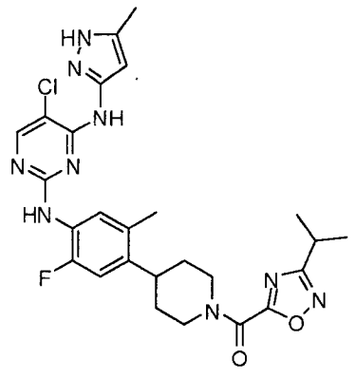
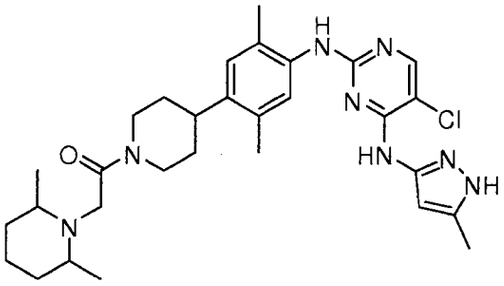
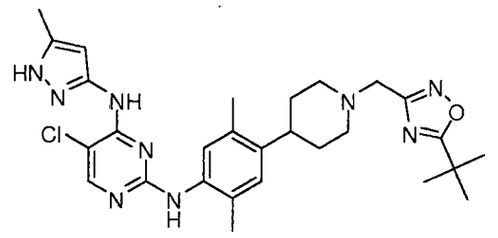
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 2-amino-1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)propan-1-one	 5-chloro-N2-(4-(1-((2,2-difluorocyclopropyl)methyl)piperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-methyl-2-(methylamino)propan-1-one	 5-chloro-N2-(4-(1-cyclopropylpiperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

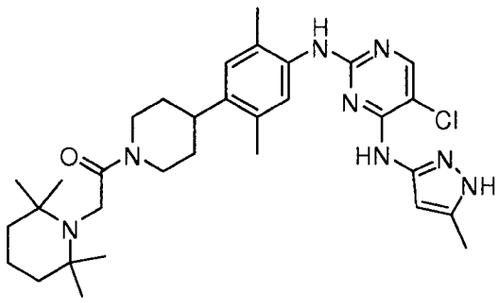
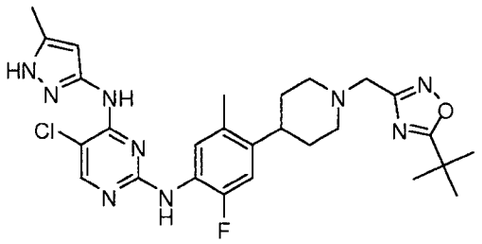
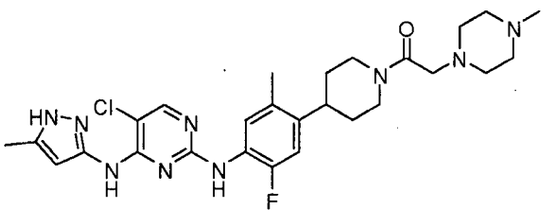
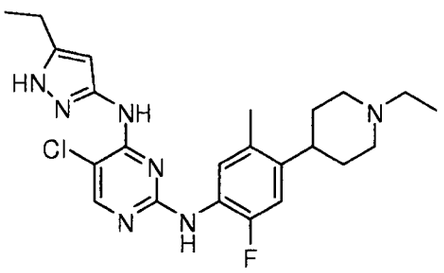
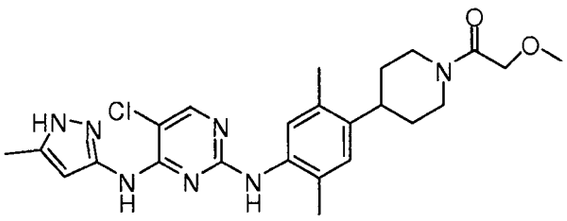
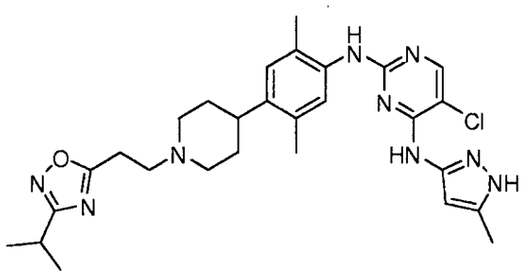
 1-(4-(2-chloro-4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-methylphenyl)piperidin-1-yl)-2-methyl-2-(methylamino)propan-1-one	 N2-(4-(1-((2,2-difluorocyclopropyl)methyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine
 2-amino-1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-methylpropan-1-one	 5-chloro-N2-(2,5-dimethyl-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)(1-(methylamino)cyclopropyl)methanone	 5-chloro-N2-(2-fluoro-4-(piperidin-4-yl)-5-(trifluoromethyl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

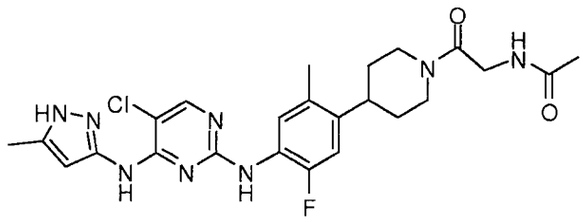
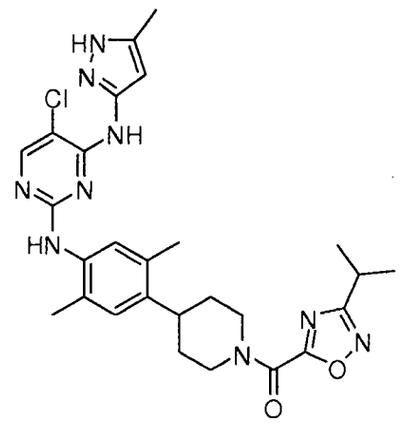
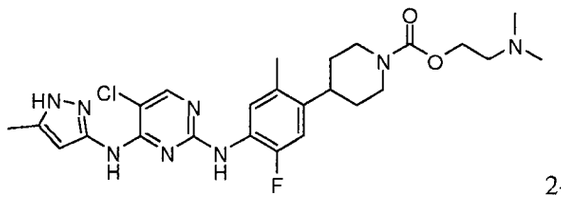
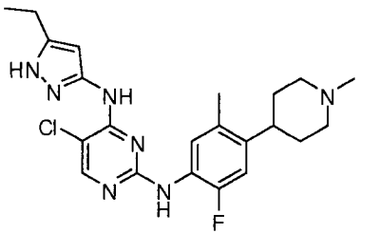
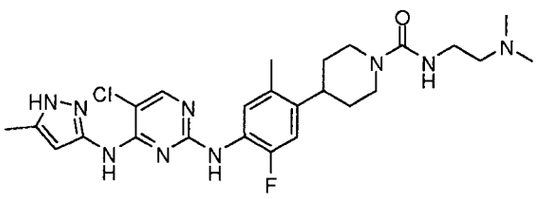
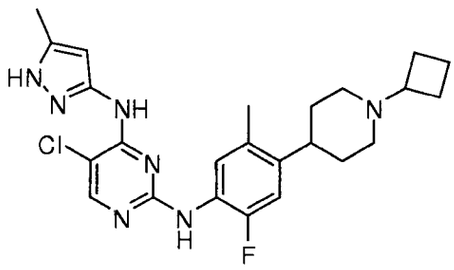
 (1-aminocyclobutyl)(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)methanone	 5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)-N2-(2-methyl-4-(piperidin-4-yl)-5-(trifluoromethyl)phenyl)pyrimidine-2,4-diamine
 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)(1-(dimethylamino)cyclobutyl)methanone	 5-chloro-N4-(5-cyclopropyl-1H-pyrazol-3-yl)-N2-(4-(1-cyclopropylpiperidin-4-yl)-2-fluoro-5-methylphenyl)pyrimidine-2,4-diamine
 (1-aminocyclopropyl)(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)methanone	 5-chloro-N2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-(dimethylamino)cyclopropyl)methanone	 N2-(2,5-dimethyl-4-(piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine

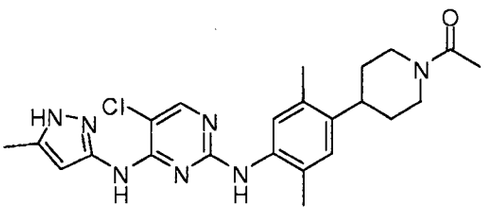
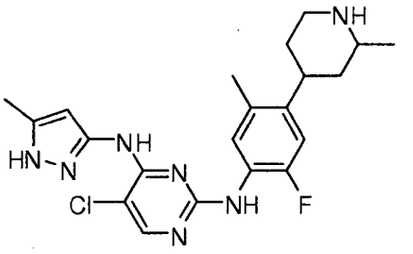
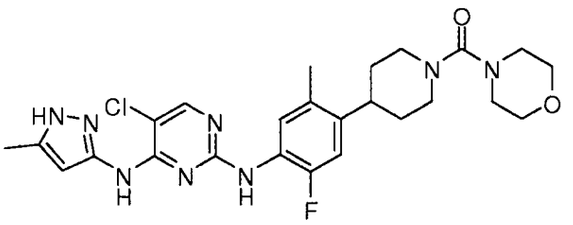
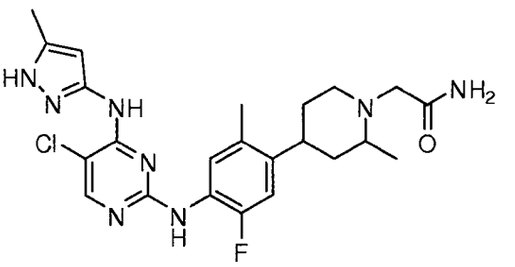
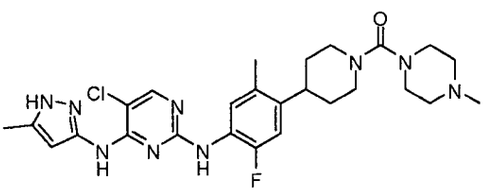
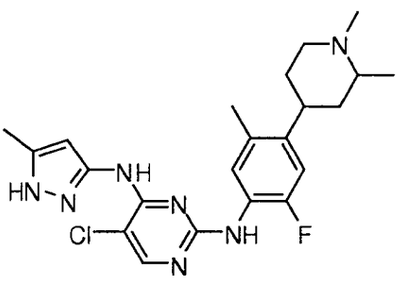
 1-(4-(2-chloro-4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-methylphenyl)piperidin-1-yl)-2-morpholinoethanone	 5-chloro-N4-(5-cyclopropyl-1H-pyrazol-3-yl)-N2-(4-(1-cyclopropylpiperidin-4-yl)-2,5-dimethylphenyl)pyrimidine-2,4-diamine
 2-(azetidin-1-yl)-1-(4-(2-chloro-4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-methylphenyl)piperidin-1-yl)ethanone	 5-chloro-N2-(2-fluoro-4-(1-((3-isopropyl-1,2,4-oxadiazol-5-yl)methyl)piperidin-4-yl)-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-morpholinoethanone	 5-chloro-N2-(4-(1-((3-isopropyl-1,2,4-oxadiazol-5-yl)methyl)piperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

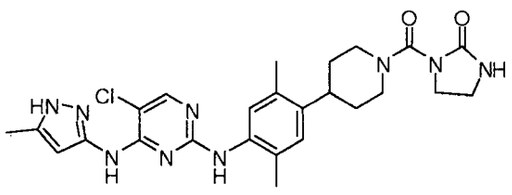
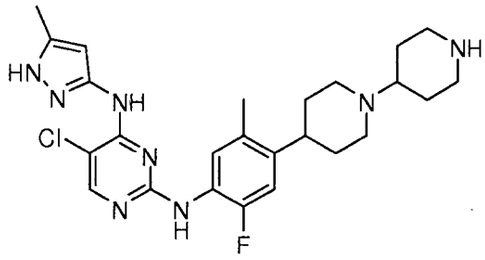
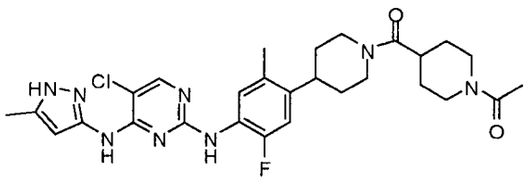
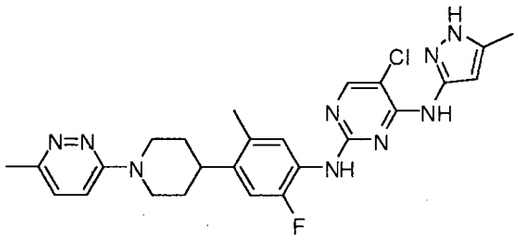
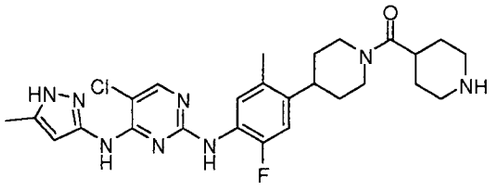
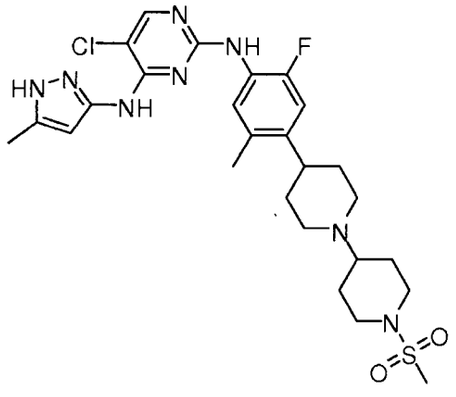
 2-(azetidin-1-yl)-1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)ethanone	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2-ethyl-5-methylphenyl)piperidin-1-yl)acetamide
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(pyrrolidin-1-yl)ethanone	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2-methoxy-5-methylphenyl)piperidin-1-yl)acetamide
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(1H-pyrrol-1-yl)ethanone	 2-(4-(4-(5-chloro-4-(5-ethyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)acetamide

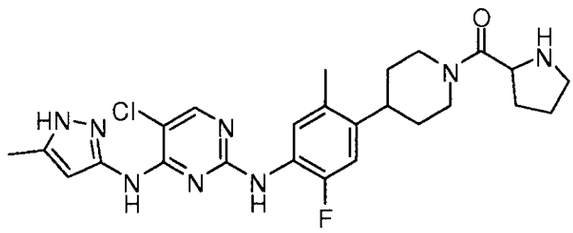
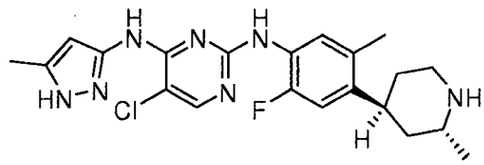
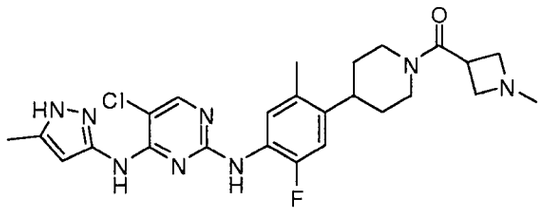
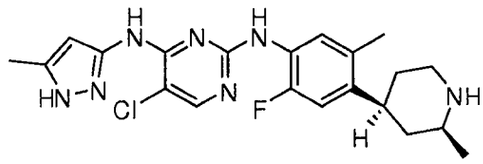
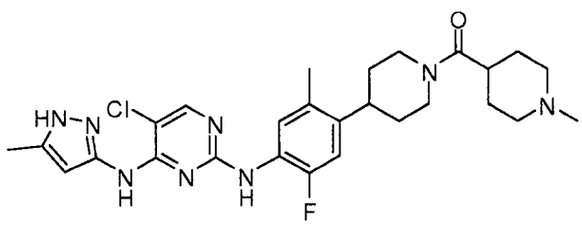
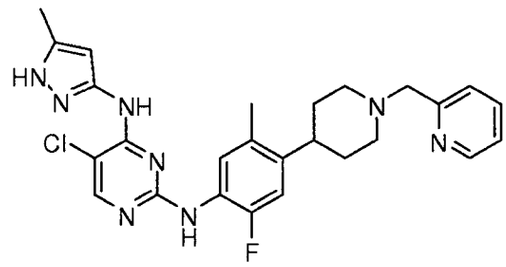
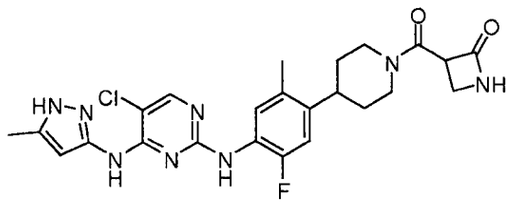
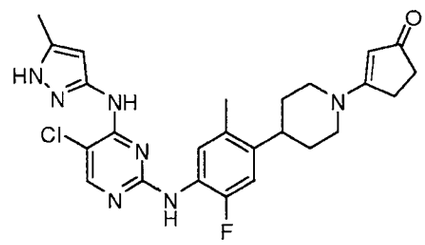
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(piperidin-1-yl)ethanone	 5-Chloro-N2-{4-[1-(1,1-dioxo-1λ6-thietan-3-yl)-piperidin-4-yl]-2-fluoro-5-methyl-phenyl}-N4-(5-ethyl-1H-pyrazol-3-yl)-pyrimidine-2,4-diamine
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-morpholinoethanone	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(3-isopropyl-1,2,4-oxadiazol-5-yl)methanone
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(2,6-dimethylpiperidin-1-yl)ethanone	 N2-(4-(1-((5-tert-butyl-1,2,4-oxadiazol-3-yl)methyl)piperidin-4-yl)-2,5-dimethylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

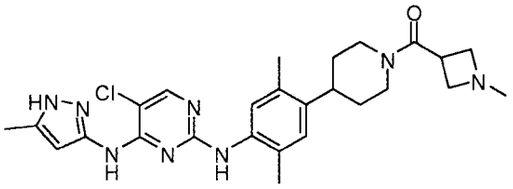
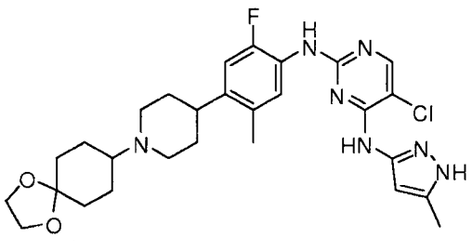
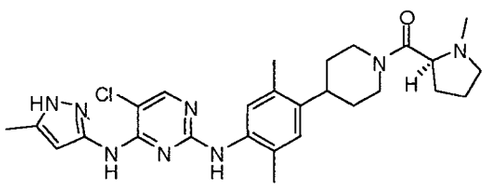
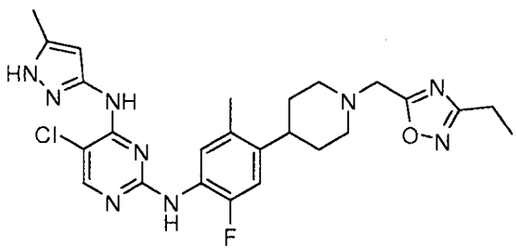
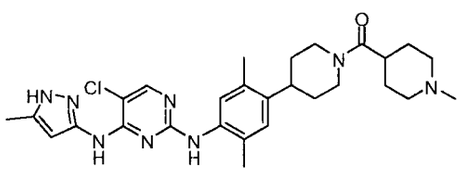
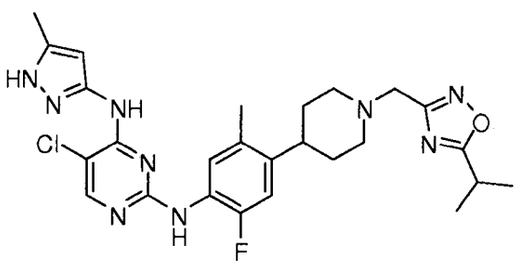
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-(2,2,6,6-tetramethylpiperidin-1-yl)ethanone	 N2-(4-(1-((5-tert-butyl-1,2,4-oxadiazol-3-yl)methyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-(4-methylpiperazin-1-yl)ethanone	 5-chloro-N4-(5-ethyl-1H-pyrazol-3-yl)-N2-(4-(1-ethylpiperidin-4-yl)-2-fluoro-5-methylphenyl)pyrimidine-2,4-diamine
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-methoxyethanone	 5-chloro-N2-(4-(1-(2-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl)piperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

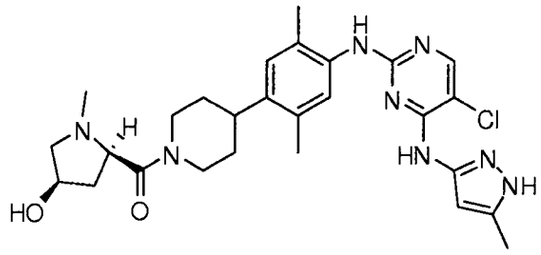
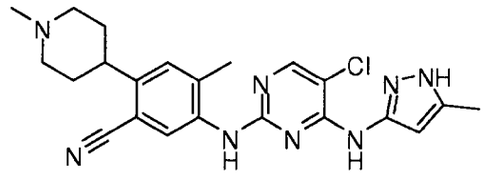
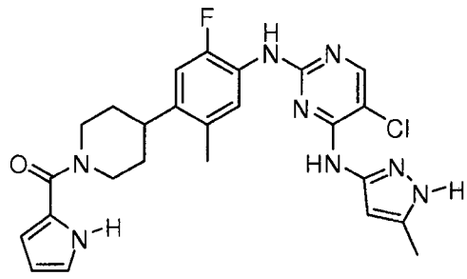
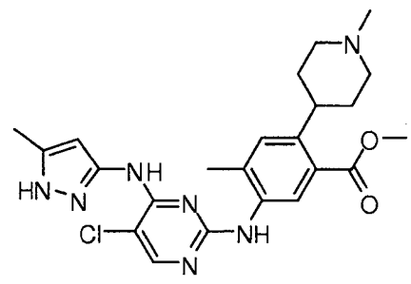
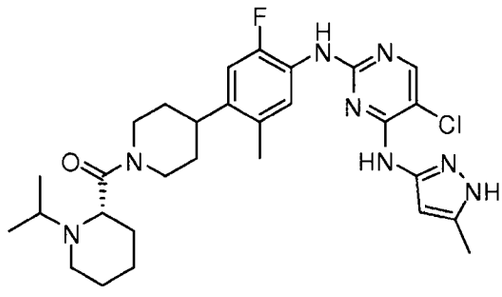
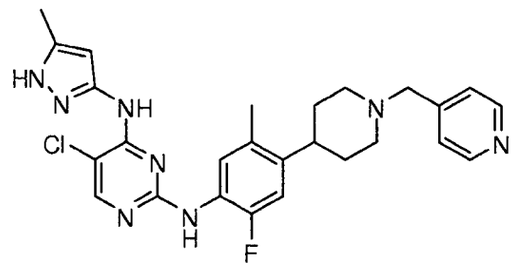
 N-(2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)-2-oxoethyl)acetamide	 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)(3-isopropyl-1,2,4-oxadiazol-5-yl)methanone
 2-(dimethylamino)ethyl 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidine-1-carboxylate	 5-chloro-N4-(5-ethyl-1H-pyrazol-3-yl)-N2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)pyrimidine-2,4-diamine
 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)-N-(2-(dimethylamino)ethyl)piperidine-1-carboxamide	 5-chloro-N2-(4-(1-cyclobutylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

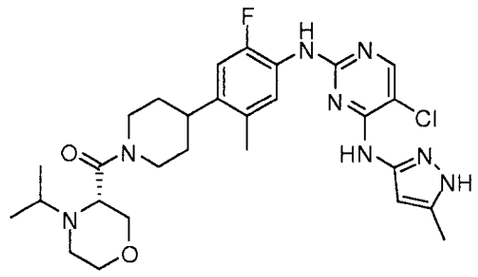
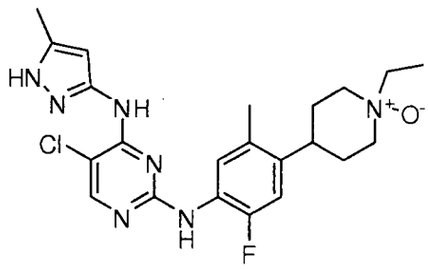
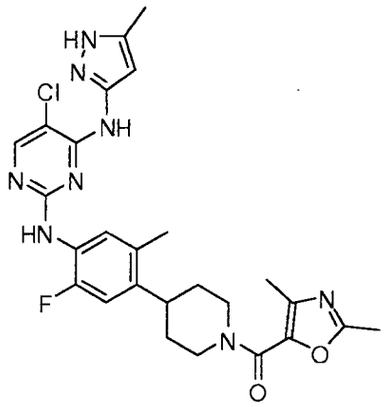
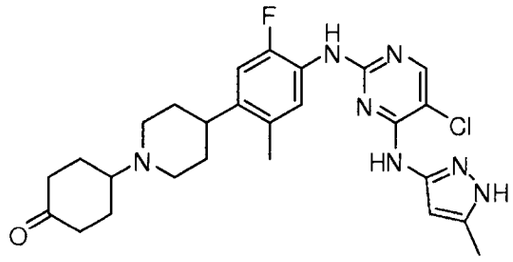
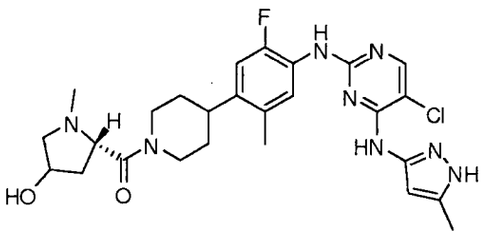
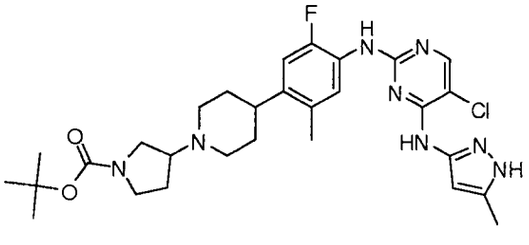
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)ethanone	 5-chloro-N2-(2-fluoro-5-methyl-4-(2-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(morpholino)methanone	 2-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)-2-methylpiperidin-1-yl)acetamide
 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(4-methylpiperazin-1-yl)methanone	 5-chloro-N2-(4-(1,2-dimethylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

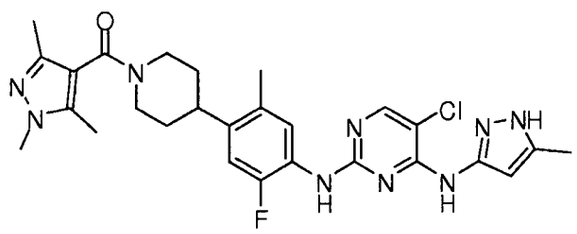
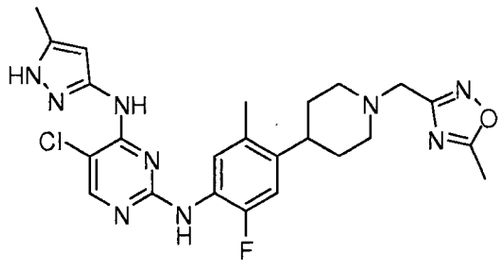
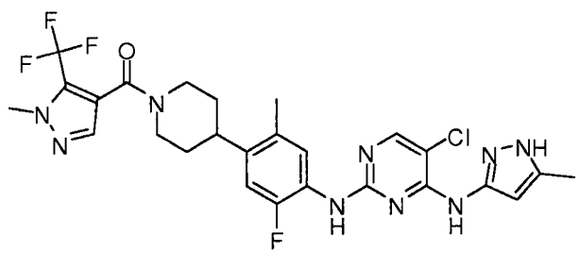
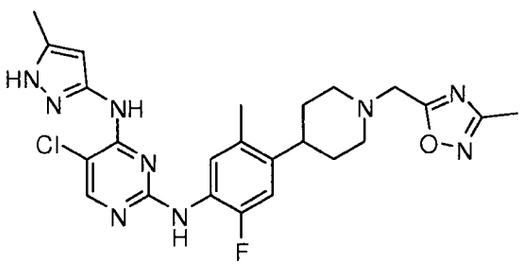
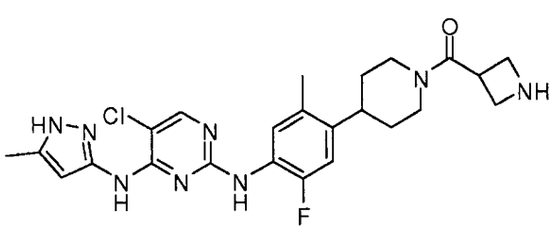
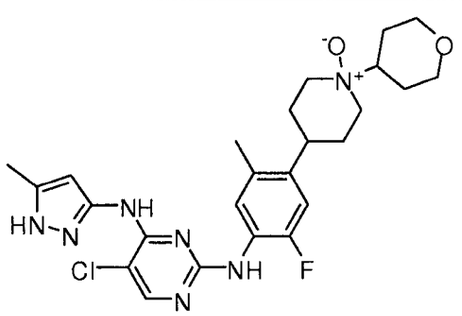
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidine-1-carbonyl)imidazolidin-2-one	 N2-(4-(1,4'-bipiperidin-4-yl)-2-fluoro-5-methylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 1-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)-2-methoxyethanone	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(6-methylpyridazin-3-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(piperidin-4-yl)methanone	 5-chloro-N2-(2-fluoro-5-methyl-4-(1'-(methylsulfonyl)-1,4'-bipiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

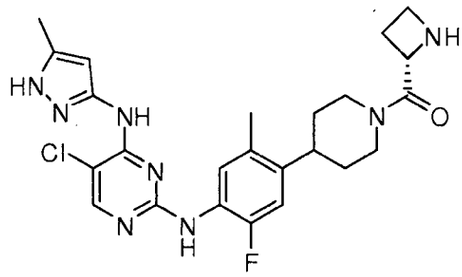
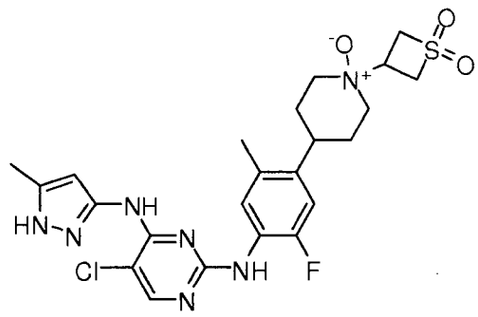
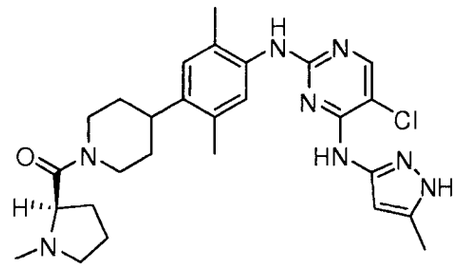
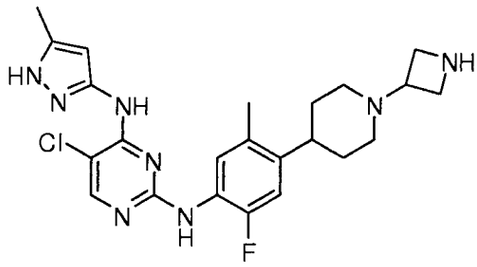
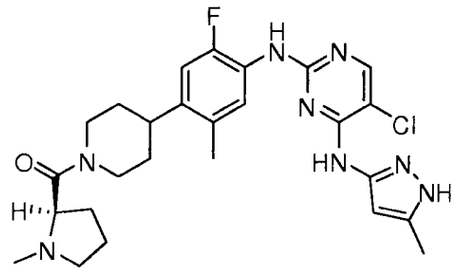
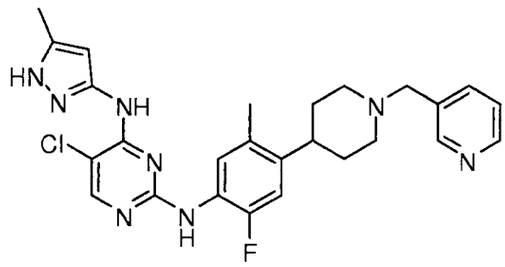
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 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-methylazetidin-3-yl)methanone	 5-chloro-N2-(2-fluoro-5-methyl-4-((cis)-2-methylpiperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-methylpiperidin-4-yl)methanone	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(pyridin-2-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidine-1-carbonyl)azetidin-2-one	 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)cyclopent-2-enone

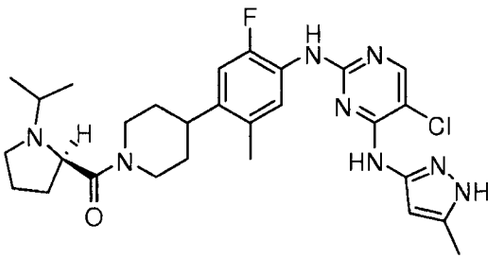
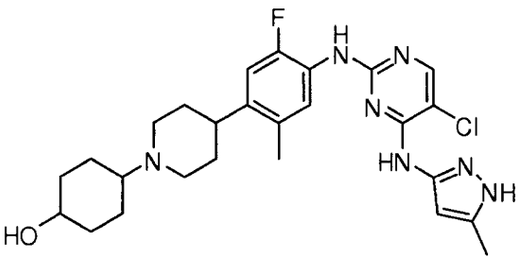
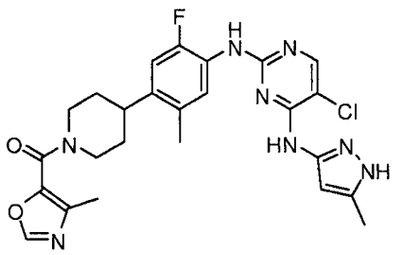
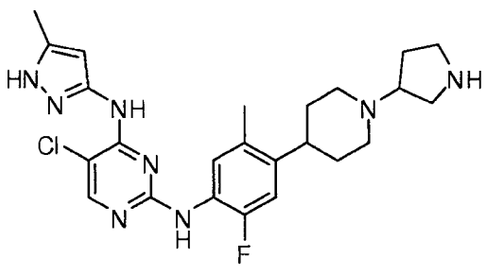
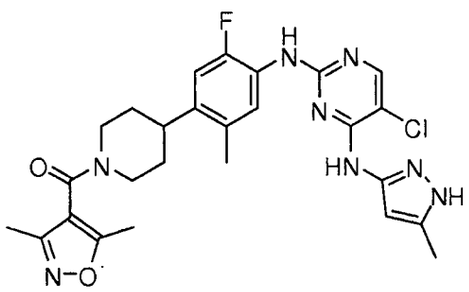
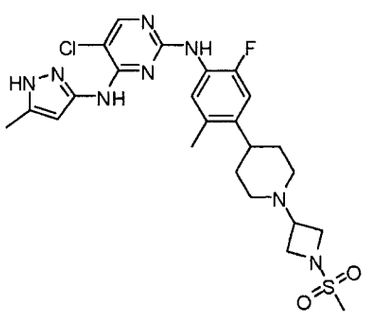
 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)(1-methylazetidin-3-yl)methanone	 N2-(4-(1-(1,4-dioxaspiro[4.5]decan-8-yl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 (*S*)-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)(1-methylpyrrolidin-2-yl)methanone	 5-chloro-N2-(4-(1-((3-ethyl-1,2,4-oxadiazol-5-yl)methyl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-1-yl)(1-methylpiperidin-4-yl)methanone	 5-chloro-N2-(2-fluoro-4-(1-((5-isopropyl-1,2,4-oxadiazol-3-yl)methyl)piperidin-4-yl)-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

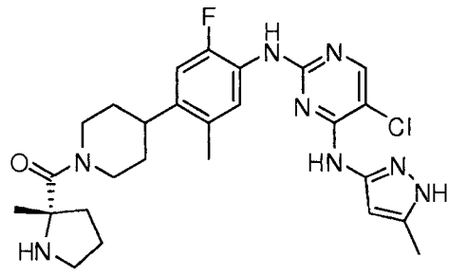
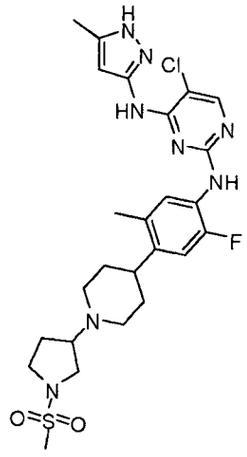
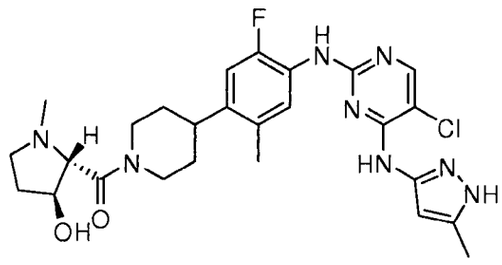
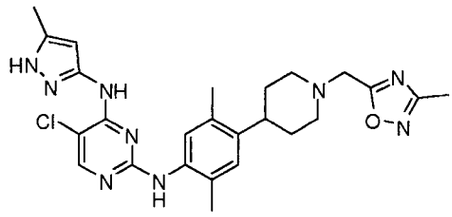
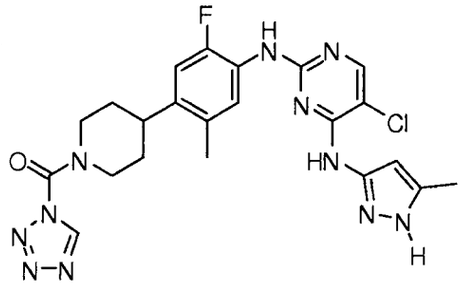
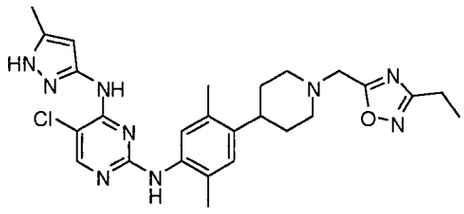
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 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1H-pyrrol-2-yl)methanone	 methyl 5-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-4-methyl-2-(1-methylpiperidin-4-yl)benzoate
 (S)-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-isopropylpiperidin-2-yl)methanone	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(pyridin-4-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

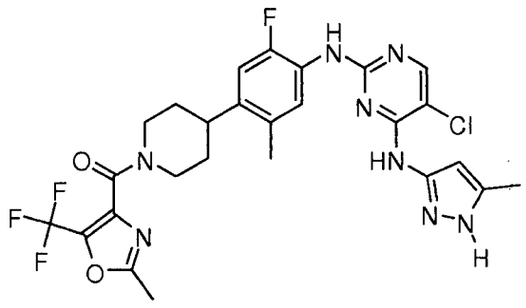
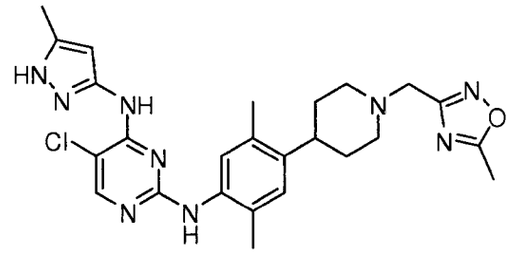
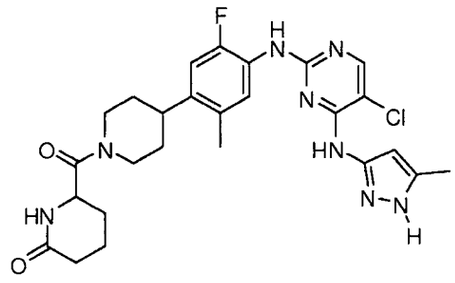
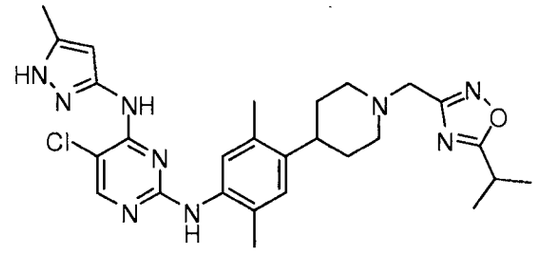
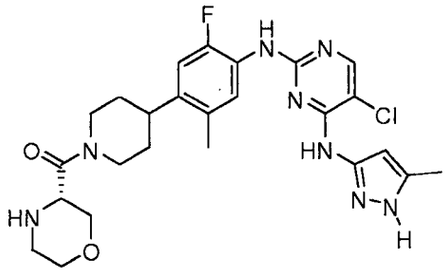
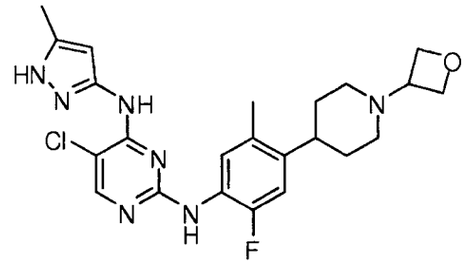
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 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(2,4-dimethyloxazol-5-yl)methanone	 4-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)cyclohexanone
 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)((2S)-4-hydroxy-1-methylpyrrolidin-2-yl)methanone	 tert-butyl 3-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)pyrrolidine-1-carboxylate

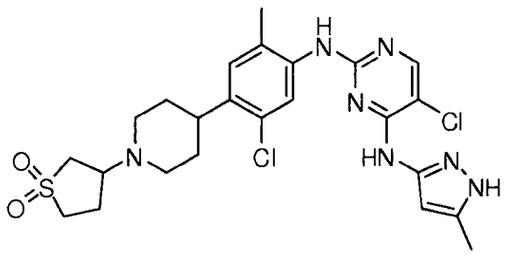
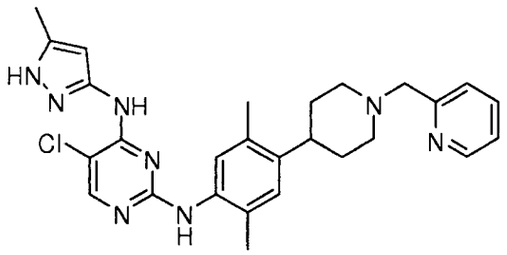
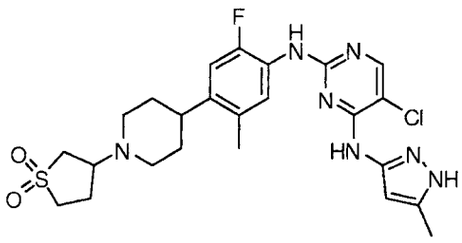
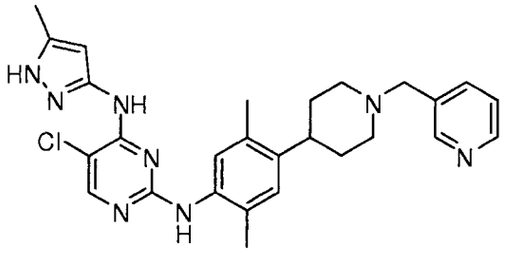
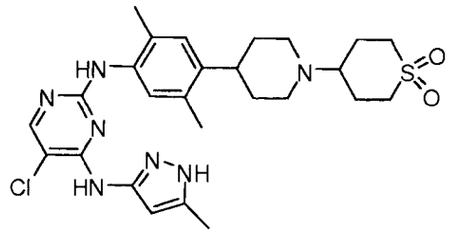
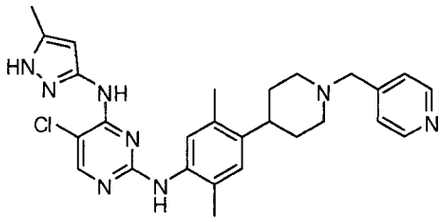
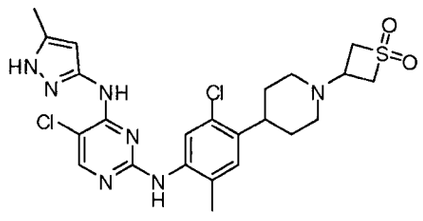
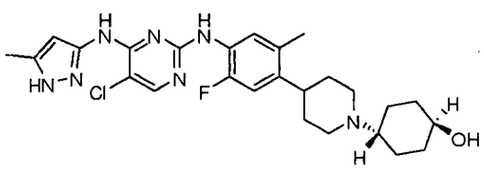
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 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)methanone	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 azetidin-3-yl(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)methanone	 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)-1-(tetrahydro-2H-pyran-4-yl)piperidine 1-oxide

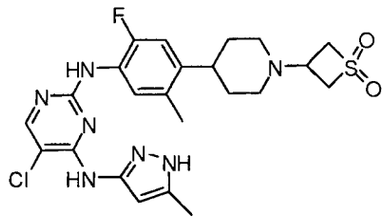
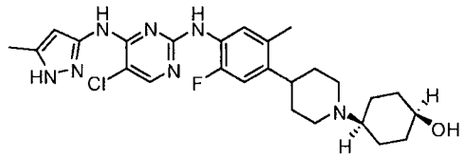
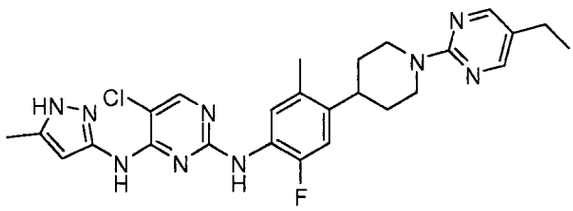
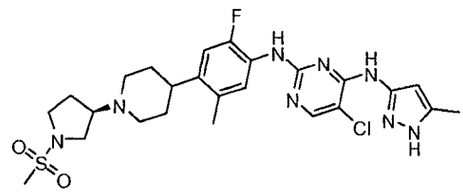
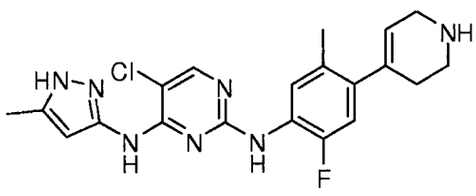
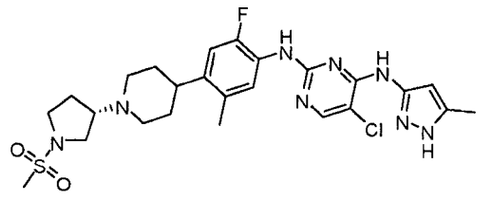
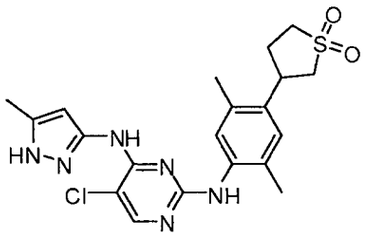
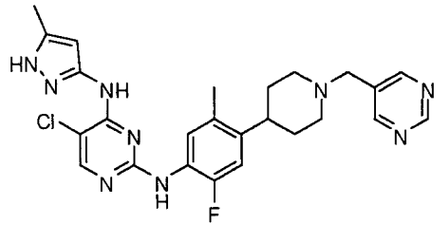
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 (R)-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl) piperidin-1-yl)(1-methylpyrrolidin-2-yl)methanone	 N2-(4-(1-(azetidin-3-yl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 (R)-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl) piperidin-1-yl)(1-methylpyrrolidin-2-yl)methanone	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(pyridin-3-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

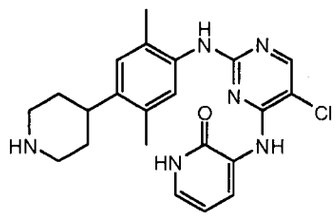
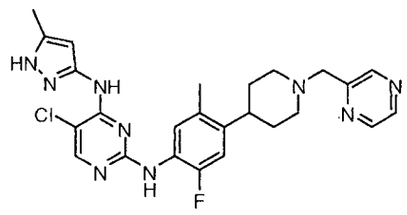
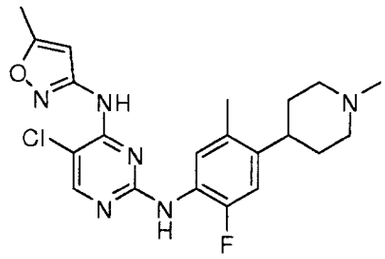
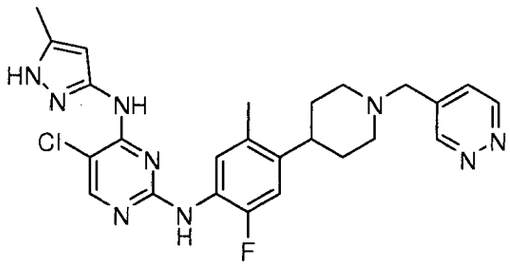
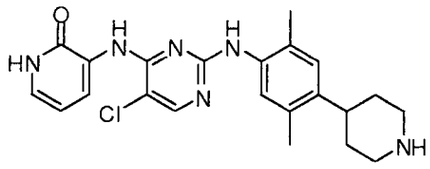
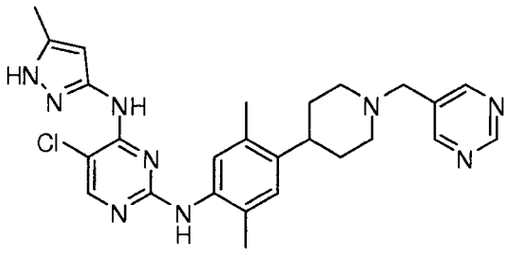
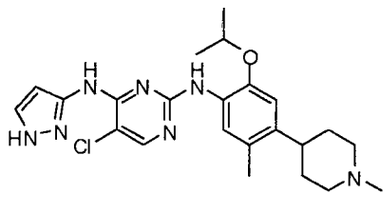
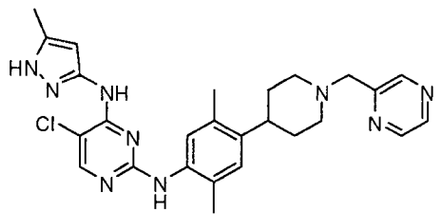
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 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(4-methyloxazol-5-yl)methanone	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(pyrrolidin-3-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(3,5-dimethylisoxazol-4-yl)methanone	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(1-(methylsulfonyl)azetidin-3-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

 (S)-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(2-methylpyrrolidin-2-yl)methanone	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(1-(methylsulfonyl)pyrrolidin-3-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)((2S,3R)-3-hydroxy-1-methylpyrrolidin-2-yl)methanone	 5-chloro-N2-(2,5-dimethyl-4-(1-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 (4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(1H-tetrazol-1-yl)methanone	 5-chloro-N2-(4-(1-((3-ethyl-1,2,4-oxadiazol-5-yl)methyl)piperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

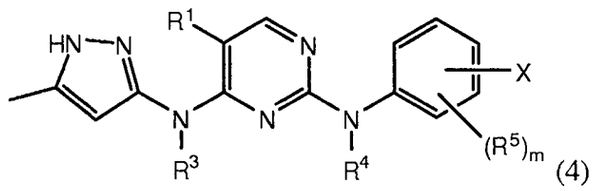
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 6-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidine-1-carbonyl)piperidin-2-one	 5-chloro-N2-(4-(1-((5-isopropyl-1,2,4-oxadiazol-3-yl)methyl)piperidin-4-yl)-2,5-dimethylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 (S)-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)(morpholin-3-yl)methanone	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(oxetan-3-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

 5-chloro-N^2-(2-methyl-5-chloro-4-(1-(tetrahydro-1,1-dioxido-3-thienyl)piperidin-4-yl)phenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine	 5-chloro-N2-(2,5-dimethyl-4-(1-(pyridin-2-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 5-chloro-N^2-(2-fluoro-5-methyl-4-(1-(tetrahydro-1,1-dioxido-3-thienyl)piperidin-4-yl)phenyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine	 5-chloro-N2-(2,5-dimethyl-4-(1-(pyridin-3-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 5-chloro-N2-(2,5-dimethyl-4-(1-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl))piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 5-chloro-N2-(2,5-dimethyl-4-(1-(pyridin-4-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 5-chloro-N2-(2-chloro-5-methyl-4-(1-(1,1-dioxido-3-thietanyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 Trans-4-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)cyclohexanol

 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(1,1-dioxido-3-thietanyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 Cis-4-(4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-5-fluoro-2-methylphenyl)piperidin-1-yl)cyclohexanol
 5-chloro-N2-(4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-2-fluoro-5-methylphenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 (R)-5-chloro-N2-(2-fluoro-5-methyl-4-(1-(1-(methylsulfonyl)pyrrolidin-3-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 5-chloro-N2-(2-fluoro-5-methyl-4-(1,2,3,6-tetrahydropyridin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 (S)-5-chloro-N2-(2-fluoro-5-methyl-4-(1-(1-(methylsulfonyl)pyrrolidin-3-yl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 5-Chloro-N^2-[4-(1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl)-2,5-dimethyl-phenyl]-N^4-(5-methyl-1*H*-pyrazol-3-yl)-pyrimidine-2,4-diamine	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(pyrimidin-5-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

 3-(5-chloro-2-(2,5-dimethyl-4-(piperidin-4-yl)phenylamino)pyrimidin-4-ylamino)pyridin-2(1H)-one	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(pyrazin-2-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 5-chloro-N2-(2-fluoro-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(5-methylisoxazol-3-yl)pyrimidine-2,4-diamine	 5-chloro-N2-(2-fluoro-5-methyl-4-(1-(pyridazin-4-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 3-(5-chloro-2-(2,5-dimethyl-4-(piperidin-4-yl)phenylamino)pyrimidin-4-ylamino)pyridin-2(1H)-one	 5-chloro-N2-(2,5-dimethyl-4-(1-(pyrimidin-5-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 5-chloro-N2-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N4-(1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 5-chloro-N2-(2,5-dimethyl-4-(1-(pyrazin-2-ylmethyl)piperidin-4-yl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine

11. A compound of Formula (4):



(4)

or a physiologically acceptable salt thereof;

wherein X is a monocyclic 5-6 membered heterocyclic ring containing 1-3 heteroatoms selected from N, O and S, and optionally substituted on a substitutable ring carbon with oxo and at any substitutable ring nitrogen by R^6;

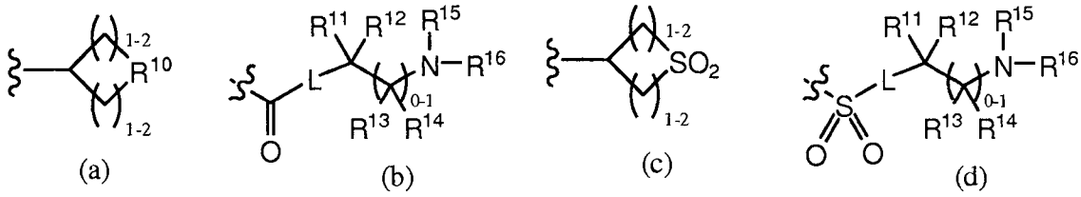
R^1 is halo;

R^3 and R^4 are each H;

R^5 is halo, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted C_{1-6} alkyl, halo-substituted C_{1-6} alkoxy, cyano or $C(O)O_{0-1}R^8$;

R^6 is H; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo and/or hydroxyl groups; $-(CR_2)_p-OR^7$, $-(CR_2)_p-CH(OH)C_tF_{2t+1}$ wherein t is 1-3, $(CR_2)_p-CN$; $(CR_2)_p-NR(R^7)$, $-(CR_2)_p-C(O)OR^7$, $(CR_2)_pNR(CR_2)_pOR^7$,
$(CR_2)_pNR-L-C(O)R^8$, $C(O)(CR_2)_qOR^8$, $-C(O)O-(CR_2)_p-NRR^7$, $-C(O)-(CR_2)_p-OR^7$, L-Y,
$-L-C(O)R^7$, $-L-C(O)-NRR^7$, $-L-C(O)-NR-(CR_2)_p-NRR^7$, $-L-C(O)NR(CR_2)_pOR^7$,
$-L-C(O)-(CR_2)_q-NR-C(O)-R^8$, $-L-C(O)NR(CR_2)_pSR^7$, $-L-C(O)NR(CR_2)_pS(O)_{1-2}R^8$,
$-L-S(O)_2R^8$, $-L-S(O)_2-(CR_2)_q-NRR^7$, $-L-S(O)_2NR(CR_2)_pNR(R^7)$ or
$-L-S(O)_2NR(CR_2)_pOR^7$;

alternatively, R^6 is a radical selected from formula (a), (b), (c) or (d):



(a) (b) (c) (d)

R^{10} is O, S, NR^{17} wherein R^{17} is H, C_{1-6} alkyl, SO_2R^{8a} or CO_2R^{8a};

R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are independently selected from H; C_{1-6} alkoxy; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino or hydroxyl groups; or R^{11} and R^{12}, R^{12} and R^{15}, R^{15} and R^{16}, R^{13}

and R^{14}, or R^{13} and R^{15} together with the atoms to which they are attached may form a 3-7 membered saturated, unsaturated or partially unsaturated ring containing 1-3 heteroatoms selected from N, O and S, and optionally substituted with oxo and 1-3 R^5 groups;

L is $(CR_2)_{1-4}$ or a bond;

Y is C_{3-7} carbocyclic ring, C_{6-10} aryl, or a 5-10 membered heteroaryl or 4-10 membered heterocyclic ring, each of which is optionally substituted with 1-3 R^5 groups;

R^7, R^8 and R^{8a} are independently C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino, hydroxyl or cyano; $(CR_2)_qY$ or C_{1-6} alkoxy; or R^7 is H;

each R is independently H or C_{1-6} alkyl;

R and R^7 together with N in each NRR^7 may form a 5-6 membered ring containing 1-3 heteroatoms selected from N, O and S, and optionally substituted with oxo and 1-3 R^5 groups;

m is 2-4;

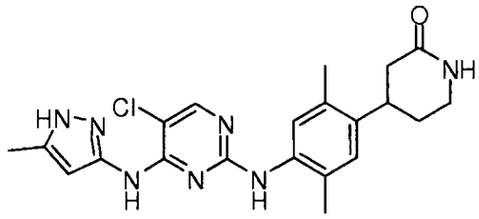
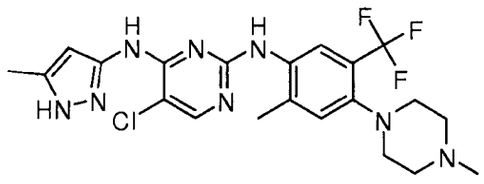
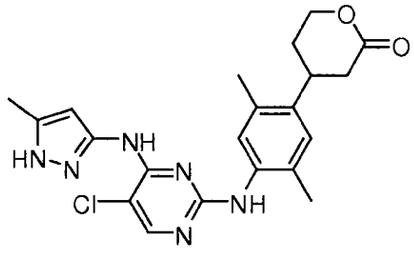
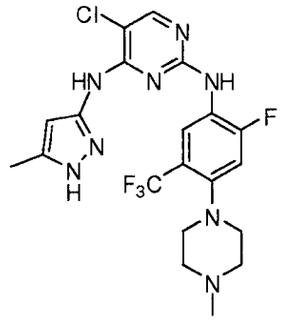
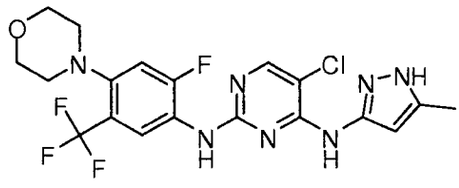
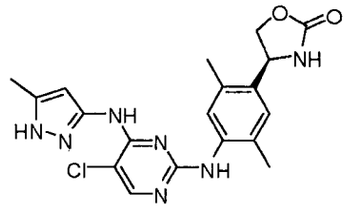
n is 1-3;

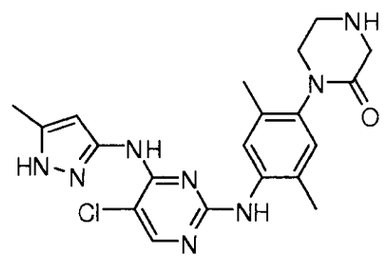
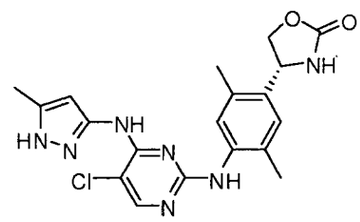
p is 1-4; and

q is 0-4.

12. The compound of claim 11, wherein X is morpholinyl, piperazinyl, piperazin-2-onyl, oxazolidin-2-onyl or piperidin-2-onyl each of which is substituted at any substitutable ring nitrogen by C_{1-6} alkyl; or X is tetrahydro-2H-pyran-2-onyl; and R^1 is chloro.

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

 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperidin-2-one	 5-chloro-N4-(5-methyl-1H-pyrazol-3-yl)-N2-(2-methyl-4-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)pyrimidine-2,4-diamine
 4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)tetrahydro-2H-pyran-2-one	 5-chloro-N2-(2-fluoro-4-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine
 5-chloro-N2-(2-fluoro-4-morpholino-5-(trifluoromethyl)phenyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	 (S)-4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)oxazolidin-2-one

	
1-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)piperazin-2-one	(R)-4-(4-(5-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-ylamino)-2,5-dimethylphenyl)oxazolidin-2-one

14. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1-13 and a physiologically acceptable carrier.

15. A method for inhibiting IGF-1R in a cell, comprising contacting the cell with an effective amount of a compound of any one of claims 1-13 or a pharmaceutical composition thereof.

16. A method for treating an IGF-1R-mediated condition in a mammal suffering therefrom, comprising administering to the mammal a therapeutically effective amount of a compound of any one of claims 1-13 or a pharmaceutical composition thereof, 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.

17. The method of claim 16, wherein said condition is a cell proliferative disorder.

18. The method of claim 17, wherein said cell proliferative disorder is multiple myeloma, neuroblastoma, synovial, hepatocellular, Ewing's Sarcoma or a solid tumor selected from a osteosarcoma, melanoma, and tumor of breast, renal, prostate, colorectal, thyroid, ovarian, pancreatic, lung, uterine or gastrointestinal tumor.

19. The method of claim 16, wherein said second therapeutic agent is a

chemotherapeutic agent.

20. The use of a compound of any one of claims 1-13, or a pharmaceutical composition thereof, for the manufacture of a medicament for treating a condition mediated by IGF-1R or 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.

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(81) **Estados (Países) Designados** (*a menos que se indique de otra manera, para cada tipo de protección nacional disponible*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, 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, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

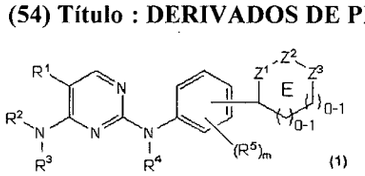
(84) **Estados (Países) Designados** (*a menos que se indique de otra manera, para cada tipo de protección regional disponible*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasiáticos (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europeos (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaraciones de acuerdo con la Regla 4.17:
-- *de inventoría (Regla 4.17(iv))*

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-- *con reporte de búsqueda internacional (Art. 21(3))*
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(54) Título : DERIVADOS DE PIRIMIDINA COMO INHIBIDORES DE CINASA



(1)

(57) Resumen:

La invención proporciona novedosos derivados de pirimidina de la fórmula I y composiciones farmacéuticas de los mismos, y métodos para utilizar estos compuestos. Por ejemplo, los derivados de pirimidina de la invención se pueden utilizar para tratar, aminorar o prevenir una condición que responda a la inhibición del factor de crecimiento tipo insulina (IGF-1R) o de la cinasa de linfoma anaplásico (ALK).

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11-008053

DERIVADOS DE PIRIMIDINA COMO INHIBIDORES DE CINASA

Referencia Cruzada con Solicitudes Relacionadas

Esta solicitud reivindica el beneficio de las Solicitudes Provisionales de Patente de los Estados Unidos de Norteamérica con Números de Serie 61/075,583, presentada el 25 de junio de 2008, y 61/155,434, presentada el 25 de febrero de 2009, cada una de las cuales se incorpora a la presente como referencia en su totalidad.

Campo Técnico

La invención se refiere a inhibidores de cinasa de proteína, más particularmente, a novedosos derivados de pirimidina y a composiciones farmacéuticas de los mismos, y a su uso como productos farmacéuticos.

Técnica Antecedente

La señalización del factor de crecimiento tipo insulina (IGF-1) está altamente implicada en el cáncer, con el receptor de IGF-1 (IGF-1R) como el factor predominante. IGR-1R es importante para la transformación del tumor y la sobrevivencia de las células malignas, pero solamente está parcialmente involucrado en el crecimiento de las células normales. Se ha sugerido que la dirección hacia el IGF-1R es una opción prometedora para la terapia de cáncer. (Larsson y colaboradores, Br. J. Cancer 92: 2097-2101 (2005)).

La cinasa de linfoma anaplásico (ALK), un miembro de la súper familia de receptores de insulina de las cinasas de tirosina receptoras, se ha implicado en la oncogénesis en los tumores

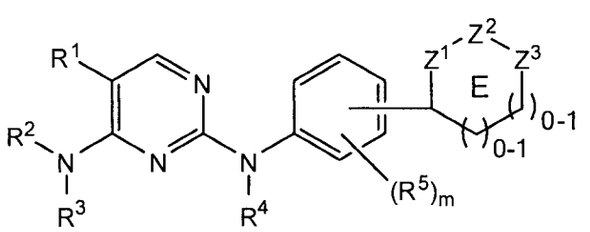
hematopoiéticos y no hematopoiéticos. Se ha reportado la expresión aberrante de las proteínas del receptor ALK de longitud completa en los neuroblastomas y glioblastomas; y se han presentado proteínas de fusión de ALK en el linfoma macrocelular anaplásico. El estudio de las proteínas de fusión de ALK también ha presentado la posibilidad de nuevos tratamientos terapéuticos para los pacientes con malignidades positivas para ALK. (Pulford y colaboradores, Cell. Mol. Life Sci. 61: 2939-2953 (2004)).

Debido a los papeles relacionados con enfermedad que están surgiendo de IGF-1R y ALK, existe una necesidad continua de compuestos que puedan ser útiles para el tratamiento y la prevención de una enfermedad que responda a la inhibición de IGF-1R y ALK.

Descripción de la Invención

La invención se refiere a novedosos derivados de pirimidina y a composiciones farmacéuticas de los mismos, y a su uso como productos farmacéuticos.

En un aspecto, la invención proporciona un compuesto de la fórmula (1):



(1)

o una sal fisiológicamente aceptable del mismo;

en donde el anillo E puede contener opcionalmente un doble enlace;

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uno de Z^1, Z^2 y Z^3 es NR^6, $N(R^6)^+$-O^- o $S(O)_{1-2}$ y los otros son CR_2;

R^1 es halógeno o un alquilo de 1 a 6 átomos de carbono opcionalmente halogenado;

R^2 es piridin-2-onilo, azepan-2-onilo o un heteroarilo monocíclico de 5 a 6 miembros que tiene de 1 a 3 heteroátomos seleccionados a partir de N, O y S; cada uno de los cuales está opcionalmente sustituido con R^9 en donde R^9 es alquilo de 1 a 6 átomos de carbono, halo-alquilo de 1 a 6 átomos de carbono, o cicloalquilo de 3 a 7 átomos de carbono;

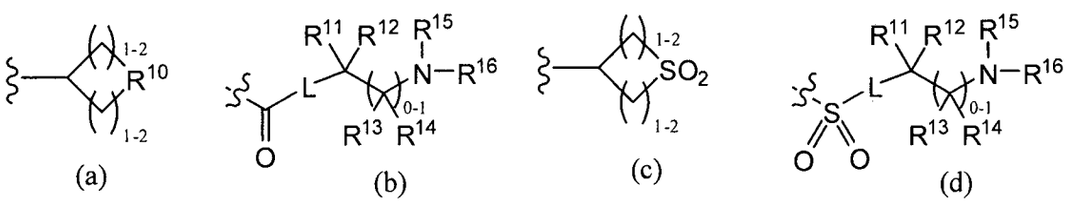
R^3 y R^4 son cada uno H;

R^5 es halógeno, hidroxilo, alquilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno, ciano o $C(O)O_{0-1}R^8$;

R^6 es H; alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con grupos halógeno y/o hidroxilo; $-(CR_2)_p-OR^7$, $-(CR_2)_p-CH(OH)C_tF_{2t+1}$ en donde t es de 1 a 3, $(CR_2)_p-CN$; $(CR_2)_p-NR(R^7)$, $-(CR_2)_p-C(O)OR^7$, $(CR_2)_pNR(CR_2)_pOR^7$, $(CR_2)_pNR-L-C(O)R^8$, $C(O)-(CR_2)_qOR^8$, $-C(O)O-(CR_2)_p-NRR^7$, $-C(O)-(CR_2)_p-OR^7$, L-Y, $-L-C(O)R^7$, $-L-C(O)-NRR^7$, $-L-C(O)-NR-(CR_2)_p-NRR^7$, $-L-C(O)NR(CR_2)_pOR^7$, $-L-C(O)-(CR_2)_q-NR-C(O)-R^8$, $-L-C(O)NR(CR_2)_pSR^7$, $-L-C(O)NR(CR_2)_pS(O)_{1-2}R^8$, $-L-S(O)_2R^8$, $-L-S(O)_2-(CR_2)_q-NRR^7$, $-L-S(O)_2NR(CR_2)_pNR(R^7)$ o -L-

$S(O)_2NR(CR_2)_pOR^7$;

de una manera alternativa, R^6 es un radical seleccionado a partir de la fórmula (a), (b), (c) o (d):



(a) (b) (c) (d)

R^{10} es O, S, NR^{17} en donde R^{17} es H, alquilo de 1 a 6 átomos de carbono, SO_2R^{8a} o CO_2R^{8a};

R^{11}, R^{12}, R^{13}, R^{14}, R^{15} y R^{16} se seleccionan independientemente a partir de H; alcoxilo de 1 a 6 átomos de carbono; alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con grupos halógeno, amino, o hidroxilo; o R^{11} y R^{12}, R^{12} y R^{15}, R^{15} y R^{16}, R^{13} y R^{14}, o R^{13} y R^{15}, junto con los átomos con los que están unidos, pueden formar un anillo de 3 a 7 miembros, saturado, insaturado, o parcialmente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O, y S, y opcionalmente sustituido con oxo y de 1 a 3 grupos R^5;

L es $(CR_2)_{1-4}$ o un enlace;

Y es un anillo carbocíclico de 3 a 7 átomos de carbono, arilo de 6 a 10 átomos de carbono, o un heteroarilo de 5 a 10 miembros o anillo heterocíclico de 4 a 10 miembros, cada uno de los cuales está opcionalmente sustituido con 1 a 3 grupos R^5;

R^7, R^8 y R^{8a} son independientemente alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con halógeno, amino, hidroxilo o ciano; $(CR_2)_qY$ o alcoxilo de 1 a 6 átomos de carbono; o R^7 es H;

cada R es independientemente H o alquilo de 1 a 6 átomos de carbono;

R y R^7 junto con N en cada NRR^7 pueden formar un anillo de 5 a 6 miembros que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O, y S, y opcionalmente sustituido con oxo y de 1 a 3 grupos R^5;

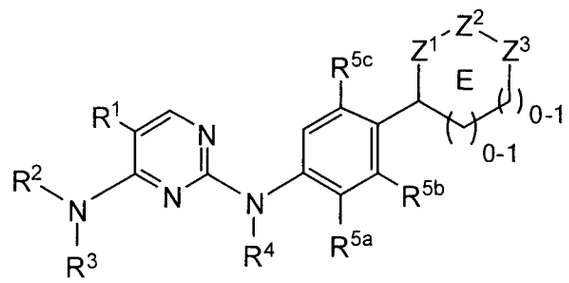
m es de 2 a 4;

n es de 1 a 3;

p es de 1 a 4; y

q es de 0 a 4.

En una modalidad, la invención proporciona un compuesto es de la fórmula (2):



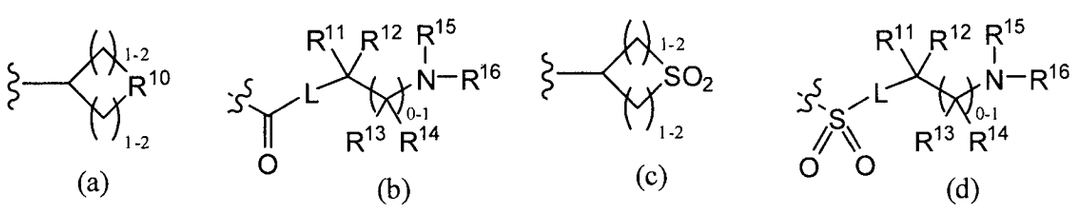
(2)

en donde uno de R^{5a}, R^{5b} y R^{5c} es H, y los otros son independientemente halógeno, alquilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de

carbono sustituido por halógeno, ciano o $C(O)O_{0-1}R^8$ en donde R^8 es alquilo de 1 a 6 átomos de carbono; y

R^1, R^2, R^3, R^4, E, Z^1, Z^2 y Z^3 son como se definen en la fórmula (1).

En algunos ejemplos, Z^3 en la fórmula (2) anterior es NR^6 o $N(R^6)^+$-O^-; y Z^1 y Z^2 son CH_2. En otros ejemplos, R^6 es H, alquilo de 1 a 6 átomos de carbono opcionalmente sustituido con grupos halógeno y/o hidroxilo; $-(CR_2)_p-OR^7$, $-(CR_2)_p-CH(OH)C_tF_{2t+1}$ en donde t es de 1 a 3, L-Y, $(CR_2)_p-CN$; $(CR_2)_p-NR(R^7)$, $-(CR_2)_p-C(O)OR^7$, $C(O)-(CR_2)_qOR^8$, $-C(O)O-(CR_2)_p-NRR^7$, $-L-C(O)R^7$, $-L-C(O)-NRR^7$, $-L-C(O)-NR-(CR_2)_p-NRR^7$, $-L-C(O)-(CR_2)_q-NR-C(O)-R^8$, $-L-S(O)_2R^8$, $-L-S(O)_2-(CR_2)_q-NRR^7$, o un radical seleccionado a partir de la fórmula (a), (b), (c) o (d):



(a) (b) (c) (d)

R^{10} es O, S, NR^{17} en donde R^{17} es H, alquilo de 1 a 6 átomos de carbono, SO_2R^{8a} o CO_2R^{8a};

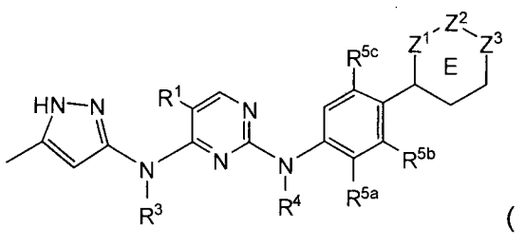
R^{8a} es alquilo de 1 a 6 átomos de carbono; y

R^7, R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R, L, Y, p y q son como se definen en la fórmula (1).

En las fórmulas (1) y (2) anteriores, R^2 puede ser pirazolilo, isoxazolilo, piridin-2-onilo o azepan-2-onilo, cada uno de los cuales está sustituido con alquilo de 1 a 6 átomos de carbono, halo-alquilo

de 1 a 6 átomos de carbono, o cicloalquilo de 3 a 7 átomos de carbono.

En otra modalidad, la invención proporciona un compuesto de la fórmula (3):



(3)

o un tautómero del mismo;

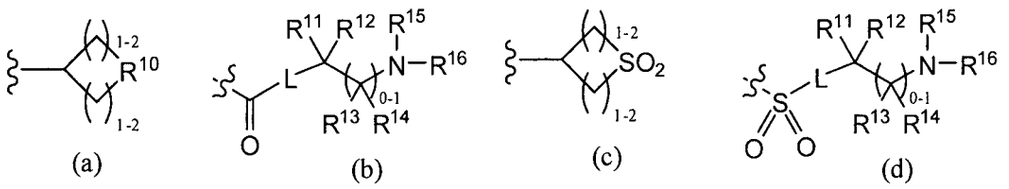
en donde R^{5b} es H; y R^{5a} y R^{5c} son independientemente halógeno, alquilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, ciano o $C(O)O_{0-1}R^8$ en donde R^8 es alquilo de 1 a 6 átomos de carbono;

Z^1 y Z^2 son CH^2;

Z^3 es NR^6 o $N(R^6)^+$-O^-;

R^6 es H, alquilo de 1 a 6 átomos de carbono opcionalmente sustituido con grupos halógeno y/o hidroxilo;

-$(CR_2)_p$-OR^7, -$(CR_2)_p$-$CH(OH)C_tF_{2t+1}$ en donde t es de 1 a 3, $(CR_2)_p$-CN; $(CR_2)_p$-$NR(R^7)$, -$(CR_2)_p$–$C(O)OR^7$, $C(O)$-$(CR_2)_qOR^8$, -$C(O)O$-$(CR_2)_p$-NRR^7, L-Y, -L-$C(O)R^7$, -L–$C(O)$-NRR^7, -L–$C(O)$-NR-$(CR_2)_p$-NRR^7, -L–$C(O)$-$(CR_2)_q$-NR-$C(O)$-R^8, -L-$S(O)_2R^8$, -L-$S(O)_2$-$(CR_2)_q$-NRR^7, o un radical seleccionado a partir de la fórmula (a), (b), (c) o (d):



(a) (b) (c) (d)

R^{10} es O, S, NR^{17} en donde R^{17} es H, alquilo de 1 a 6 átomos de carbono, SO_2R^{8a} o CO_2R^{8a};

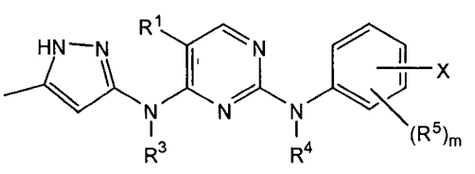
R^{8a} es alquilo de 1 a 6 átomos de carbono; y

R^1, R^3, R^4, R^7, R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R, L, Y, p, q y E son como se definen en la fórmula (1).

En la fórmula (3) anterior, R^{5a} puede ser halógeno y R^{5c} es alquilo de 1 a 6 átomos de carbono. En algunos ejemplos, R^6 es alquilo de 1 a 6 átomos de carbono, o a un radical de la fórmula (a) o (c); y R^{10} es O.

En las fórmulas (1), (2), y (3) anteriores, R^1 puede ser halógeno. En los ejemplos particulares, R^1 es cloro. En otros ejemplos, R^3 y R^4 son H.

En otro aspecto, la presente invención proporciona un compuesto de la fórmula (4):



(4)

o una sal fisiológicamente aceptable del mismo;

en donde X es un anillo heterocíclico monocíclico de 5 a 6 miembros que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O, y S, y opcionalmente sustituido sobre un átomo de carbono

del anillo sustituible con oxo y en cualquier átomo de nitrógeno del anillo sustituible por R^6;

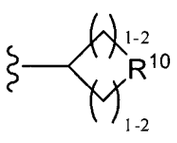
R^1 es halógeno;

R^3 y R^4 son cada uno H;

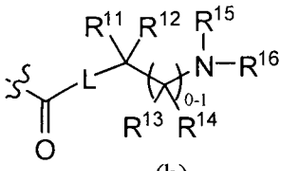
R^5 es halógeno, hidroxilo, alquilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno, ciano o $C(O)O_{0-1}R^8$;

R^6 es H; alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con grupos halógeno y/o hidroxilo; $-(CR_2)_p-OR^7$, $-(CR_2)_p-CH(OH)C_tF_{2t+1}$ en donde t es de 1 a 3, $(CR_2)_p-CN$; $(CR_2)_p-NR(R^7)$, $-(CR_2)_p-C(O)OR^7$, $(CR_2)_pNR(CR_2)_pOR^7$, $-(CR_2)_pNR-L-C(O)R^8$, $C(O)-(CR_2)_qOR^8$, $-C(O)O-(CR_2)_p-NRR^7$, $-C(O)-(CR_2)_p-OR^7$, L-Y, $-L-C(O)R^7$, $-L-C(O)-NRR^7$, $-L-C(O)-NR-(CR_2)_p-NRR^7$, $-L-C(O)NR(CR_2)_pOR^7$, $-L-C(O)-(CR_2)_q-NR-C(O)-R^8$, $-L-C(O)NR(CR_2)_pSR^7$, $-L-C(O)NR(CR_2)_pS(O)_{1-2}R^8$, $-L-S(O)_2R^8$, $-L-S(O)_2-(CR_2)_q-NRR^7$, $-L-S(O)_2NR(CR_2)_pNR(R^7)$ o $-L-S(O)_2NR(CR_2)_pOR^7$;

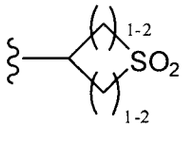
de una manera alternativa, R^6 es un radical seleccionado a partir de la fórmula (a), (b), (c) o (d):



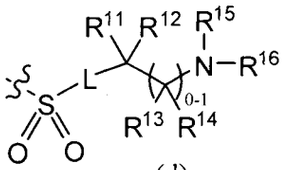
(a)



(b)



(c)



(d)

R^{10} es O, S, NR^{17} en donde R^{17} es H, alquilo de 1 a 6 átomos de carbono, SO_2R^{8a} o CO_2R^{8a};

R^{11}, R^{12}, R^{13}, R^{14}, R^{15} y R^{16} se seleccionan independientemente a partir de H; alcoxilo de 1 a 6 átomos de carbono; alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con grupos halógeno, amino, o hidroxilo; o R^{11} y R^{12}, R^{12} y R^{15}, R^{15} y R^{16}, R^{13} y R^{14}, o R^{13} y R^{15}, junto con los átomos con los que están unidos, pueden formar un anillo de 3 a 7 miembros, saturado, insaturado, o parcialmente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O, y S, y opcionalmente sustituido con oxo y de 1 a 3 grupos R^5;

L es $(CR_2)_{1-4}$ o un enlace;

Y es un anillo carbocíclico de 3 a 7 átomos de carbono, arilo de 6 a 10 átomos de carbono, o un heteroarilo de 5 a 10 miembros o anillo heterocíclico de 4 a 10 miembros, cada uno de los cuales está opcionalmente sustituido con 1 a 3 grupos R^5;

R^7, R^8 y R^{8a} son independientemente alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con halógeno, amino, hidroxilo o ciano; $(CR_2)_qY$ o alcoxilo de 1 a 6 átomos de carbono; o R^7 es H;

cada R es independientemente H o alquilo de 1 a 6 átomos de carbono;

R y R^7 junto con N en cada NRR^7 pueden formar un anillo de 5 a 6 miembros que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O, y S, y opcionalmente sustituido con oxo y de 1 a 3 grupos R^5;

m es de 2 a 4;

n es de 1 a 3;

p es de 1 a 4; y

q es de 0 a 4.

En la fórmula (4) anterior, X puede ser morfolinilo, piperazinilo, piperazin-2-onilo, oxazolidin-2-onilo o piperidin-2-onilo, cada uno de los cuales está sustituido en cualquier átomo de nitrógeno del anillo sustituible por alquilo de 1 a 6 átomos de carbono; o X es tetrahidro-2H-piran-2-onilo; y R^1 es cloro.

En otro aspecto, la presente invención proporciona las composiciones farmacéuticas que comprenden un compuesto que tiene la fórmula (1), (2), (3), y (4), y un excipiente fisiológicamente aceptable.

En todavía otro aspecto, la invención proporciona métodos para inhibir IGF-1R en una célula, los cuales comprenden poner en contacto la célula con una cantidad efectiva de un compuesto que tiene la fórmula (1), (2), (3), y (4) o una composición farmacéutica del mismo.

La invención también proporciona métodos para tratar, aminorar, o prevenir una condición que responda a la inhibición de IGF-1R o cinasa de linfoma anaplásico (ALK) en un mamífero que

sufra de esta condición, los cuales comprenden administrar al mamífero una cantidad terapéuticamente efectiva de un compuesto que tiene la fórmula (1), (2), (3), y (4), o una composición farmacéutica del mismo, y opcionalmente en combinación con un segundo agente terapéutico. De una manera alternativa, la presente invención proporciona el uso de un compuesto que tiene la fórmula (1), (2), (3), y (4), y opcionalmente en combinación con un segundo agente terapéutico, en la fabricación de un medicamento para el tratamiento de una condición mediada por IGF-1R o ALK. Los compuestos de la invención se pueden administrar, por ejemplo, a un mamífero que sufra de una enfermedad autoinmune, una enfermedad por trasplante, una enfermedad infecciosa, o un trastorno proliferativo celular. En los ejemplos particulares, los compuestos de la invención se pueden utilizar solos o en combinación con un agente quimioterapéutico para tratar un trastorno proliferativo celular, incluyendo, pero no limitándose a, mieloma múltiple, neuroblastoma, sarcoma sinovial, hepatocelular, de Ewing, o un tumor sólido seleccionado a partir de un osteosarcoma, melanoma, y tumor de mama, renal, de próstata, colo-rectal, de tiroides, de ovario, pancreático, de pulmón, uterino, o un tumor gastrointestinal.

Definiciones

"Alquilo" se refiere a una fracción, y como un elemento estructural de otros grupos, por ejemplo alquilo y alcoxilo sustituidos por halógeno, y puede ser de cadena recta o ramificada. Un alquilo, alquenilo o alquinilo opcionalmente sustituido, como se utiliza en la

presente, puede estar opcionalmente halogenado (por ejemplo, CF_3), o puede tener uno o más átomos de carbono sustituidos o reemplazados con un heteroátomo, tal como NR, O o S (por ejemplo, $-OCH_2CH_2O-$, tioalquilos, tioalcoxilo, alquil-aminas, etc.).

"Arilo" se refiere a un anillo aromático monocíclico o bicíclico fusionado que contiene átomos de carbono. "Arileno" significa un radical divalente derivado a partir de un grupo arilo. Por ejemplo, un grupo arilo puede ser fenilo, indenilo, indanilo, naftilo, o 1,2,3,4-tetrahidro-naftalenilo, el cual puede estar opcionalmente sustituido en la posición *orto, meta,* o *para*.

"Heteroarilo", como se utiliza en la presente, es como se define para arilo anteriormente, en donde uno o más de los miembros del anillo es un heteroátomo. Por ejemplo, un sustituyente de heteroarilo para utilizarse en los compuestos de la invención puede ser un heteroarilo monocíclico o bicíclico de 5 a 10 miembros que contiene de 1 a 4 heteroátomos seleccionados a partir de N, O, y S. Los ejemplos de los heteroarilos incluyen, pero no se limitan a, piridilo, pirazinilo, indolilo, indazolilo, quinoxalinilo, quinolinilo, benzo-furanilo, benzo-piranilo, benzo-tiopiranilo, benzo-[1,3]-dioxol, imidazolilo, benzo-imidazolilo, pirimidinilo, furanilo, oxazolilo, isoxazolilo, triazolilo, benzotriazolilo, tetrazolilo, pirazolilo, tienilo, pirrolilo, isoquinolinilo, purinilo, tiazolilo, tetrazinilo, benzo-tiazolilo, oxadiazolilo, benzoxadiazolilo, etc.

Un "anillo carbocíclico", como se utiliza en la presente, se refiere a un anillo monocíclico, bicíclico fusionado, o policíclico

puenteado, saturado o parcialmente insaturado, que contiene átomos de carbono, el cual puede estar opcionalmente sustituido, por ejemplo, con =O. Los ejemplos de los anillos carbocíclicos incluyen, pero no se limitan a, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclopropileno, ciclohexanona, etc.

Un "anillo heterocíclico", como se utiliza en la presente, es como se define para un anillo carbocíclico anteriormente, en donde uno o más átomos de carbono del anillo son un heteroátomo. Por ejemplo, un anillo heterocíclico para utilizarse en los compuestos de la invención puede ser un anillo heterocíclico de 4 a 7 miembros que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O, y S, o una combinación de los mismos, tal como -S(O) o $-S(O)_2-$. Los ejemplos de los anillos heterocíclicos incluyen, pero no se limitan a, azetidinilo, morfolino, pirrolidinilo, pirrolidinil-2-ona, piperazinilo, piperidinilo, piperidinilona, 1,4-dioxa-8-aza-espiro-[4.5]-dec-8-ilo, 1,2,3,4-tetrahidro-quinolinilo, etc. Los anillos heterocíclicos, como se utilizan en la presente, pueden abarcar a las aminas bicíclicas y a las diaminas bicíclicas.

Como se utiliza en la presente, un átomo de H en cualesquiera grupos sustituyentes (por ejemplo, CH_2), abarca todas las variaciones isotópicas adecuadas, por ejemplo, H, ^2H y ^3H.

El término "combinación farmacéutica", como se utiliza en la presente, se refiere a un producto obtenido de la mezcla o combinación de los ingredientes activos, e incluye tanto las combinaciones fijas como no fijas de los ingredientes activos. El

término "combinación fija" significa que los ingredientes activos, por ejemplo, un compuesto de la fórmula (1), y un co-agente, se administran ambos a un paciente de una manera simultánea en la forma de una sola entidad o dosificación. El término "combinación no fija" significa que los ingredientes activos, por ejemplo, un compuesto de la fórmula (1), y un co-agente, se administran ambos a un paciente como entidades separadas, ya sea de una manera simultánea, concurrente, o en secuencia, sin límites de tiempo específicos, en donde esta administración proporcione niveles terapéuticamente efectivos de los ingredientes activos en el cuerpo del paciente. Esto último también se aplica a la terapia de cóctel, por ejemplo, la administración de tres o más ingredientes activos.

"Mamífero" se refiere a cualquier animal clasificado como un mamífero, incluyendo seres humanos, animales domésticos y de granja, y animales de zoológico, de deportes, o de mascota, tales como perros, gatos, reses, caballos, ovejas, cerdos, cabras, conejos, etc. En los ejemplos particulares, el mamífero es un ser humano.

El término "administración" o "administrar" al sujeto el compuesto, significa proporcionar un compuesto de la invención y pro-fármacos del mismo a un sujeto que necesite tratamiento. Administración "en combinación con" uno o más agentes terapéuticos adicionales incluye la administración simultánea (concurrente), y la administración consecutiva, en cualquier orden, y por cualquier vía de administración.

Una "cantidad efectiva" de un compuesto es una cantidad

suficiente para llevar a cabo un propósito específicamente mencionado. Una "cantidad efectiva" se puede determinar empíricamente y de una manera rutinaria, en relación con el propósito mencionado.

El término "cantidad terapéuticamente efectiva" se refiere a una cantidad de un compuesto (por ejemplo, un antagonista de IGF-1R) efectiva para "tratar" un trastorno mediado por IGF-1R en un sujeto o en un mamífero. En el caso del cáncer, la cantidad terapéuticamente efectiva del fármaco puede reducir el número de células de cáncer; reducir el tamaño del tumor; inhibir (es decir, hacer más lenta hasta algún grado y de preferencia detener) la infiltración de las células de cáncer hacia dentro de los órganos periféricos; inhibir (es decir, hacer más lenta hasta algún grado y de preferencia detener) la metástasis tumoral; inhibir, hasta algún grado, el crecimiento tumoral; y/o aliviar hasta algún grado uno o más de los síntomas asociados con el cáncer. Véase la definición en la presente de "tratando". Hasta el grado en que el fármaco pueda prevenir el crecimiento y/o pueda aniquilar las células de cáncer existentes, éste puede ser citostático y/o citotóxico.

El término "cáncer" se refiere a la condición fisiológica en mamíferos que se caracteriza típicamente por un crecimiento / proliferación celular no regulada. Los ejemplos de cáncer incluyen, pero no se limitan a: carcinoma, linfoma, blastoma, y leucemia. Los ejemplos más particulares de cánceres incluyen, pero no se limitan a: leucemia linfocítica crónica (CLL), cáncer de pulmón, incluyendo

cáncer pulmonar no microcelular (NSCLC), de mama, de ovario, cervical, endometrial, de próstata, colo-rectal, carcinoide intestinal, de vejiga, gástrico, pancreático, hepático (hepatocelular), hepatoblastoma, esofágico, adenocarcinoma pulmonar, mesotelioma, sarcoma sinovial, osteosarcoma, carcinoma de células escamosas de cabeza y cuello, angiofibromas nasofaríngeos juveniles, liposarcoma, tiroides, melanoma, carcinoma de células basales (BCC), meduloblastoma, y desmoideo.

"Tratando" o "tratamiento" o "alivio" se refiere al tratamiento tanto terapéutico como profiláctico, o medidas preventivas, en donde el objeto es prevenir o hacer más lenta (disminuir) la enfermedad o condición patológica o trastorno dirigido. Los que necesitan el tratamiento incluyen aquéllos que ya tienen el trastorno, así como aquéllos susceptibles a tener el trastorno, o aquéllos en quienes se deba prevenir el trastorno (profilaxis). Cuando el trastorno mediado por IGF-1R es cáncer, un sujeto o mamífero se "trata" con éxito o muestra una carga tumoral reducida si, después de recibir una cantidad terapéutica de un antagonista de IGF-1R de acuerdo con los métodos de la presente invención, el paciente muestra una reducción observable y/o mensurable en, o una ausencia de, uno o más de los siguientes: reducción en el número de células de cáncer o ausencia de las células de cáncer; reducción en el tamaño del tumor; inhibición (es decir, hacer más lenta hasta algún grado y de preferencia detener) de la infiltración de las células de cáncer hacia dentro de los órganos periféricos, incluyendo la extensión del cáncer

hacia dentro del tejido blando y del hueso; inhibición (es decir, hacer más lenta hasta algún grado y de preferencia detener) de la metástasis tumoral; inhibición, hasta algún grado, del crecimiento tumoral; y/o alivio hasta algún grado, de uno o más de los síntomas asociados con el cáncer específico; patología y mortalidad reducidas, y mejora en la calidad de vida. Hasta el grado en que el antagonista de IGF-1R pueda prevenir el crecimiento y/o aniquilar las células de cáncer existentes, éste puede ser citostático y/o citotóxico. La reducción de estos signos o síntomas también puede ser sentida por el paciente.

"Vehículos", como se utilizan en la presente, incluyen los vehículos farmacéuticamente aceptables, excipientes, o estabilizantes que no sean tóxicos para la célula o el mamífero que esté siendo expuesto a los mismos en las dosificaciones y concentraciones empleadas. Con frecuencia, el vehículo fisiológicamente aceptable es una solución acuosa reguladora del pH. Los ejemplos de los vehículos fisiológicamente aceptables incluyen reguladores, tales como fosfato, citrato, y otros ácidos orgánicos; antioxidantes, incluyendo ácido ascórbico; polipéptido de bajo peso molecular (de menos de aproximadamente 10 residuos); proteínas, tales como albúmina de suero, gelatina, o inmunoglobulinas; polímeros hidrofílicos, tales como polivinil-pirrolidona; aminoácidos, tales como glicina, glutamina, asparagina, arginina o lisina; monosacáridos, disacáridos, y otros carbohidratos, incluyendo glucosa, manosa, o dextrinas; agentes quelantes, tales

como EDTA; alcoholes de azúcar, tales como manitol o sorbitol; contra-iones formadores de sales, tales como sodio; y/o tensoactivos no iónicos, tales como TWEEN®, polietilenglicol (PEG), y PLURONICS®.

Un "agente quimioterapéutico" es un compuesto químico útil en el tratamiento de cáncer. Los ejemplos de los agentes quimioterapéuticos incluyen agentes alquilantes, tales como tiotepa y CYTOXAN® ciclosfosfamida; sulfonatos de alquilo, tales como busulfano, improsulfano y piposulfano; aziridinas, tales como benzodopa, carbocuona, meturedopa, y uredopa; etileniminas y metil-melaminas, incluyendo altretamina, trietilen-melamina, trietilen-fosforamida, trietilen-tiofosforamida y trimetilol-melamina; acetogeninas (en especial bulatacina y bulatacinona); delta-9-tetrahidro-canabinol (dronabinol, MARINOL®); beta-lapacona; lapacol; colquicinas; ácido betulínicob; una camptotecina (incluyendo el análogo sintético de topotecano (HYCAMTIN®), CPT-11 (irinotecano, CAMPTOSAR®), acetil-camptotecina, escopolectina, y 9-amino-camptotecina); briostatina; calistatina; CC-1065 (incluyendo sus análogos sintéticos de adozelesina, carzelesina y bizelesina); podofilotoxina; ácido podofilínico; teniposida; criptoficinas (en particular criptoficina 1 y criptoficina 8); dolastatina; duocarmicina (incluyendo los análogos sintéticos, KW-2189 y CB1-TM1); eleuterobina; pancratistatina; una sarcodictiina; espongistatina; mostazas de nitrógeno, tales como clorambucil, clornafazina, colofosfamida, estramustina, ifosfamida, mecloretamina, clorhidrato

de óxido de mecloretamina, melfalano, novembiquina, fenesterina, prednimustina, trofosfamida, mostaza de uracilo; nitrosureas, tales como carmustina, clorozotocina, fotemustina, lomustina, nimustina, y ranimustina; antibióticos, tales como los antibióticos de enodiina (por ejemplo, caliqueamicina, en especial caliqueamicina gammaII y caliqueamicina omegaII (véase, por ejemplo, Agnew, Chem Intl. Ed. Engl., 33: 183-186 (1994)); dinemicina, incluyendo dinemicina A; una esperamicina; así como el cromóforo neocarzinostatina y los cromóforos antibióticos de enodiina de cromoproteína relacionados), aclacinomisinas, actinomicina, autramicina, azaserina, bleomicinas, cactinomicina, carabicina, caminomicina, carzinofilina, cromomicinas, dactinomicina, daunorrubicina, detorrubicina, 6-diazo-5-oxo-L-norleucina, ADRIAMYCIN® doxorrubicina (incluyendo morfolino-doxorrubicina, ciano-morfolino-doxorrubicina, 2-pirrolino-doxorrubicina y desoxidoxorrubicina), epirrubicina, esorrubicina, idarrubicina, marcelomicina, mitomicinas, tales como mitomicina C, ácido micofenólico, nogalamicina, olivomicinas, peplomicina, potfiromicina, puromicina, quelamicina, rodorrubicina, estreptonigrina, estreptozocina, tubercidina, ubenimex, zinostatina, zorrubicina; anti-metabolitos, tales como metotrexato y 5-fluoro-uracilo (5-FU); análogos de ácido fólico, tales como denopterina, metotrexato, pteropterina, trimetrexato; análogos de purina, tales como fludarabina, 6-mercapto-purina, tiamiprina, tioguanina; análogos de pirimidina, tales como ancitabina, azacitidina, 6-azauridina, carmofur, citarabina, didesoxi-uridina, doxifluridina,

enocitabina, floxuridina; andrógenos, tales como calusterona, propionato de dromostanolona, epitiostanol, mepitiostano, testolactona; anti-adrenales, tales como amino-glutetimida, mitotano, trilostano; rellenador de ácido fólico, tal como ácido frolínico; aceglatona; glicósido de aldofosfamida; ácido amino-levulínico; eniluracilo; amsacrina; bestrabucilo; bisantreno; edatraxato; defofamina; demecolcina; diazicuona; elfomitina; acetato de eliptinio; una epotilona; etoglucida; nitrato de galio; hidroxi-urea; lentinano; lonidainina; maytansinoides, tales como maytansina y ansamitocinas; mitoguazona; mitoxantrona; mopidanmol; nitraerina; pentostatina; fenamet; pirarrubicina; losoxantrona; 2-etil-hidrazida; procarbazina; complejo de polisacárido PSK® (JHS Natural Products, Eugene, Oreg.); razoxano; rizoxina; sizofurano; espirogermanio; ácido tenuazónico; triazicuona; 2,2',2''-tricloro-trietil-amina; tricotecenos (en especial toxina T-2, verracurina A, roridina A, y anguidina); uretano; vindesina (ELDISINE®, FILDESIN®); dacarbazina; manomustina; mitobronitol; mitolactol; pipobromano; gacitosina; arabinosida ("Ara-C"); tiotepa; taxoides, por ejemplo, TAXOL® paclitaxel (Bristol-Myers Squibb Oncology, Princeton, N.J.), ABRAXANE^{MR} sin Cremophor, formulación de paclitaxel en nanopartículas diseñadas con albúmina (American Pharmaceutical Partners, Schaumberg, Ill), y docetaxel TAXOTERE® (Rhône-Poulenc Rorer, Antony, Francia); clorambucil; gemcitabina (GEMZAR®); 6-tioguanina; mercapto-purina; metotrexato; análogos de platino, tales como cisplatina y carboplatina; vinblastina (VELBAN®); platino;

etoposida (VP-16); ifosfamida; mitoxantrona; vincristina (ONCOVIN®); oxaliplatina; leucovorina; vinorelbina (NAVELBINE®); novantrona; edatrexato; daunomicina; aminopterina; ibandronato; inhibidor de topoisomerasa RFS 2000; difluoro-metil-ornitina (DMFO); retinoides, tales como ácido retinoico; capecitabina (XELODA®); sales farmacéuticamente aceptables, ácidos o derivados de cualquiera de los anteriores; así como combinaciones de dos o más de los anteriores, tales como CHOP, una abreviatura para una terapia combinada de ciclofosfamida, doxorrubicina, vincristina, y prednisolona, y FOLFOX, una abreviatura para el régimen de tratamiento con oxaliplatina (ELOXATIN^{MR}) combinada con 5-FU y leucovorina.

Adicionalmente, un "agente quimioterapéutico" puede incluir agentes anti-hormonales que actúen para regular, reducir, bloquear, o inhibir los efectos de las hormonas que pueden promover el crecimiento de cáncer, y que con frecuencia están en la forma de un tratamiento sistémico o de todo el cuerpo. Pueden ser las hormonas mismas. Los ejemplos incluyen anti-estrógenos y moduladores selectivos de los receptores de estrógeno (SERMs), incluyendo, por ejemplo, tamoxifeno (incluyendo tamoxifeno NOLVADEX®), EVISTA® raloxifeno, droloxifeno, 4-hidroxi-tamoxifeno, trioxifeno, queoxifeno, LY117018, onapristona, y toremifeno FARESTON®; anti-progesteronas; sub-reguladores de los receptores de estrógeno (ERDs); agentes que funcionan para suprimir o desactivar los ovarios, por ejemplo, agonistas de hormona liberadora de hormona

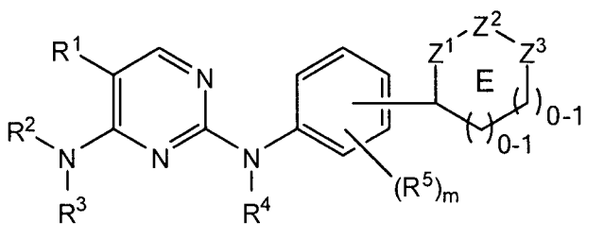
leutinizante, tales como LUPRON® y ELIGARD®, acetato de leuprolida, acetato de goserelina, acetato de buserelina, y tripterelina; otros anti-andrógenos, tales como flutamida, nilutamida y bicalutamida; e inhibidores de aromatasa que inhiben la enzima aromatasa, la cual regula la producción de estrógeno en las glándulas adrenales, tales como, por ejemplo, 4(5)-imidazoles, amino-glutetimida, acetato de megestrol MEGASE®, AROMASIN® exemestano, formestano, fadrozol, RIVISOR® vorozol, FEMARA® letrozol, y ARIMIDEX® anastrozol. En adición, esta definición de los agentes quimioterapéuticos incluye bisfosfonatos, tales como clodronato (por ejemplo, BONEFOS® u OSTAC®), DIDROCAL® etidronato, NE-58095, ZOMETA® ácido zoledrónico / /zoledronato, FOSAMAX® alendronato, AREDIA® pamidronato, SKELID® tiludronato, o ACTONEL® risedronato; así como troxacitabina (un análogo de nucleósido citosina de 1,3-dioxolano); oligonucleótidos anti-sentido, en particular aquéllos que inhiben la expresión de los genes en las sendas de señalización implicadas en la proliferación celular aberrante, tales como, por ejemplo, PKC-alfa, Raf, H-Ras, y receptor del factor de crecimiento epidérmico (EGF-R); vacunas, tales como la vacuna THERATOPE®, y vacunas de terapia genética, por ejemplo, vacuna ALLOVECTIN®, vacuna LEUVECTIN®, y vacuna VAXID®; inhibidor de topoisomerasa I LURTOTECAN®; ABARELIX® rmRH; ditosilato de lapatinib (un inhibidor de molécula pequeña de cinasa de tirosina doble de ErbB-2 y EGFR también conocido como GW572016); y las sales farmacéuticamente aceptables, ácidos o

derivados de cualquiera de los anteriores.

Modos para llevar a cabo la Invención

La invención proporciona novedosos derivados de pirimidina y composiciones farmacéuticas de los mismos, y métodos para utilizar estos compuestos.

En un aspecto, la invención proporciona un compuesto de la fórmula (1):



(1)

o una sal fisiológicamente aceptable del mismo;

en donde el anillo E puede contener opcionalmente un doble enlace;

uno de Z^1, Z^2 y Z^3 es NR^6, $N(R^6)^+\text{-}O^-$ o $S(O)_{1\text{-}2}$ y los otros son CR_2;

R^1 es halógeno o un alquilo de 1 a 6 átomos de carbono opcionalmente halogenado;

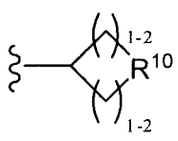
R^2 es piridin-2-onilo, azepan-2-onilo o un heteroarilo monocíclico de 5 a 6 miembros que tiene de 1 a 3 heteroátomos seleccionados a partir de N, O y S; cada uno de los cuales está opcionalmente sustituido con R^9 en donde R^9 es alquilo de 1 a 6 átomos de carbono, halo-alquilo de 1 a 6 átomos de carbono, o cicloalquilo de 3 a 7 átomos de carbono;

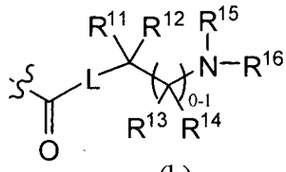
R^3 y R^4 son cada uno H;

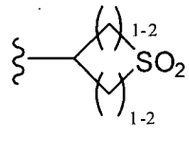
R^5 es halógeno, hidroxilo, alquilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno, ciano o $C(O)O_{0-1}R^8$;

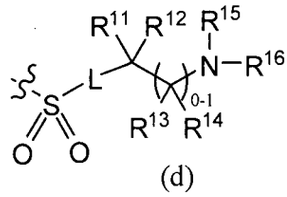
R^6 es H; alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con grupos halógeno y/o hidroxilo; $-(CR_2)_p-OR^7$, $-(CR_2)_p-CH(OH)C_tF_{2t+1}$ en donde t es de 1 a 3, $(CR_2)_p-CN$; $(CR_2)_p-NR(R^7)$, $-(CR_2)_p-C(O)OR^7$, $(CR_2)_pNR(CR_2)_pOR^7$, $(CR_2)_pNR-L-C(O)R^8$, $C(O)-(CR_2)_qOR^8$, $-C(O)O-(CR_2)_p-NRR^7$, $-C(O)-(CR_2)_p-OR^7$, L-Y, $-L-C(O)R^7$, $-L-C(O)-NRR^7$, $-L-C(O)-NR-(CR_2)_p-NRR^7$, $-L-C(O)NR(CR_2)_pOR^7$, $-L-C(O)-(CR_2)_q-NR-C(O)-R^8$, $-L-C(O)NR(CR_2)_pSR^7$, $-L-C(O)NR(CR_2)_pS(O)_{1-2}R^8$, $-L-S(O)_2R^8$, $-L-S(O)_2-(CR_2)_q-NRR^7$, $-L-S(O)_2NR(CR_2)_pNR(R^7)$ o $-L-S(O)_2NR(CR_2)_pOR^7$;

de una manera alternativa, R^6 es un radical seleccionado a partir de la fórmula (a), (b), (c) o (d):


(a)


(b)


(c)


(d)

R^{10} es O, S, NR^{17} en donde R^{17} es H, alquilo de 1 a 6 átomos de carbono, SO_2R^{8a} o CO_2R^{8a};

R^{11}, R^{12}, R^{13}, R^{14}, R^{15} y R^{16} se seleccionan independientemente a partir de H; alcoxilo de 1 a 6 átomos de carbono; alquilo de 1 a 6

átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con grupos halógeno, amino, o hidroxilo; o R^{11} y R^{12}, R^{12} y R^{15}, R^{15} y R^{16}, R^{13} y R^{14}, o R^{13} y R^{15}, junto con los átomos con los que están unidos, pueden formar un anillo de 3 a 7 miembros, saturado, insaturado, o parcialmente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O, y S, y opcionalmente sustituido con oxo y de 1 a 3 grupos R^5;

L es $(CR_2)_{1-4}$ o un enlace;

Y es un anillo carbocíclico de 3 a 7 átomos de carbono, arilo de 6 a 10 átomos de carbono, o un heteroarilo de 5 a 10 miembros o anillo heterocíclico de 4 a 10 miembros, cada uno de los cuales está opcionalmente sustituido con 1 a 3 grupos R^5;

R^7, R^8 y R^{8a} son independientemente alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con halógeno, amino, hidroxilo o ciano; $(CR_2)_qY$ o alcoxilo de 1 a 6 átomos de carbono; o R^7 es H;

cada R es independientemente H o alquilo de 1 a 6 átomos de carbono;

R y R^7 junto con N en cada NRR^7 pueden formar un anillo de 5 a 6 miembros que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O, y S, y opcionalmente sustituido con oxo y de 1 a 3 grupos R^5;

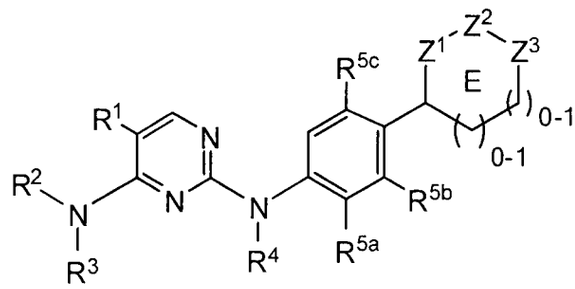
m es de 2 a 4;

n es de 1 a 3;

p es de 1 a 4; y

q es de 0 a 4.

En una modalidad, la invención proporciona un compuesto de la fórmula (2):

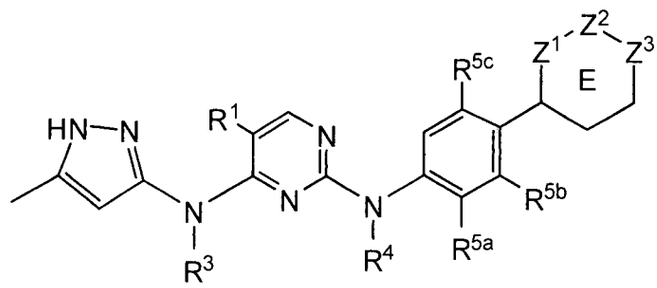


(2)

en donde uno de R^{5a}, R^{5b} y R^{5c} es H, y los otros son independientemente halógeno, alquilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, ciano o $C(O)O_{0-1}R^8$ en donde R^8 es alquilo de 1 a 6 átomos de carbono; y

R^1, R^2, R^3, R^4, E, Z^1, Z^2 y Z^3 son como se definen en la fórmula (1).

En otra modalidad, la invención proporciona un compuesto de la fórmula (3):



(3)

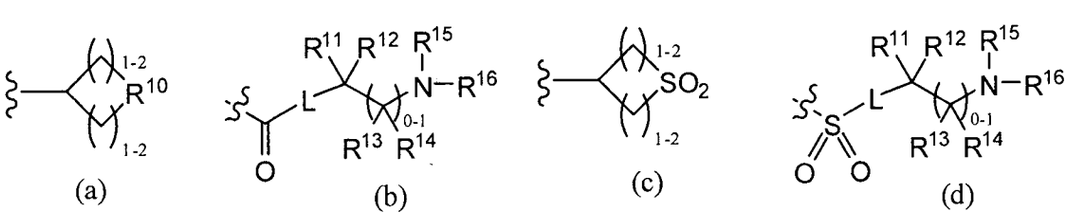
o un tautómero del mismo;

en donde R^{5b} es H; y R^{5a} y R^{5c} son independientemente halógeno, alquilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, ciano o $C(O)O_{0-1}R^8$ en donde R^8 es alquilo de 1 a 6 átomos de carbono;

Z^1 y Z^2 son CH^2;

Z^3 es NR^6 o $N(R^6)^+$-O^-;

R^6 es H, alquilo de 1 a 6 átomos de carbono opcionalmente sustituido con grupos halógeno y/o hidroxilo; $-(CR_2)_p-OR^7$, $-(CR_2)_p-CH(OH)C_tF_{2t+1}$ en donde t es de 1 a 3, $(CR_2)_p-CN$; $(CR_2)_p-NR(R^7)$, $-(CR_2)_p-C(O)OR^7$, $C(O)-(CR_2)_qOR^8$, $-C(O)O-(CR_2)_p-NRR^7$, L-Y, $-L-C(O)R^7$, $-L-C(O)-NRR^7$, $-L-C(O)-NR-(CR_2)_p-NRR^7$, $-L-C(O)-(CR_2)_q-NR-C(O)-R^8$, $-L-S(O)_2R^8$, $-L-S(O)_2-(CR_2)_q-NRR^7$, o un radical seleccionado a partir de la fórmula (a), (b), (c) o (d):



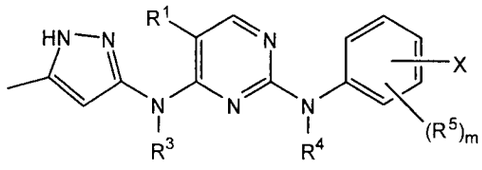
R^{10} es O, S, NR^{17} en donde R^{17} es H, alquilo de 1 a 6 átomos de carbono, SO_2R^{8a} o CO_2R^{8a};

R^{8a} es alquilo de 1 a 6 átomos de carbono; y

R^1, R^3, R^4, R^7, R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R, L, Y, p, q y E son como se definen en la fórmula (1).

En otro aspecto, la presente invención proporciona un

compuesto de la fórmula (4):



(4)

o una sal fisiológicamente aceptable del mismo;

en donde X es un anillo heterocíclico monocíclico de 5 a 6 miembros que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O, y S, y opcionalmente sustituido sobre un átomo de carbono del anillo sustituible con oxo y en cualquier átomo de nitrógeno del anillo sustituible por R^6;

R^1 es halógeno;

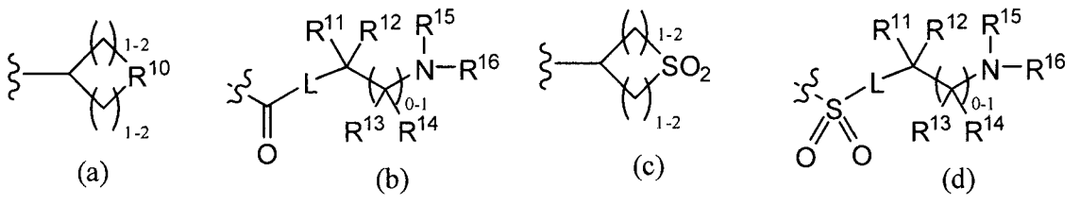
R^3 y R^4 son cada uno H;

R^5 es halógeno, hidroxilo, alquilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno, ciano o $C(O)O_{0-1}R^8$;

R^6 es H; alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con grupos halógeno y/o hidroxilo; $-(CR_2)_p-OR^7$, $-(CR_2)_p-CH(OH)C_tF_{2t+1}$ en donde t es de 1 a 3, $(CR_2)_p-CN$; $(CR_2)_p-NR(R^7)$, $-(CR_2)_p-C(O)OR^7$, $(CR_2)_pNR(CR_2)_pOR^7$, $(CR_2)_pNR-L-C(O)R^8$, $C(O)-(CR_2)_qOR^8$, $-C(O)O-(CR_2)_p-NRR^7$, $-C(O)-(CR_2)_p-OR^7$, L-Y, $-L-C(O)R^7$, $-L-C(O)-NRR^7$, $-L-C(O)-NR-(CR_2)_p-NRR^7$, $-L-C(O)NR(CR_2)_pOR^7$, $-L-C(O)-(CR_2)_q-NR-C(O)-R^8$, $-L-C(O)NR(CR_2)_pSR^7$, $-L-C(O)NR(CR_2)_pS(O)_{1-2}R^8$, -L-

$S(O)_2R^8$, -L-$S(O)_2$-$(CR_2)_q$-NRR^7, -L-$S(O)_2NR(CR_2)_pNR(R^7)$ o -L-$S(O)_2NR(CR_2)_pOR^7$;

de una manera alternativa, R^6 es un radical seleccionado a partir de la fórmula (a), (b), (c) o (d):



R^{10} es O, S, NR^{17} en donde R^{17} es H, alquilo de 1 a 6 átomos de carbono, SO_2R^{8a} o CO_2R^{8a};

R^{11}, R^{12}, R^{13}, R^{14}, R^{15} y R^{16} se seleccionan independientemente a partir de H; alcoxilo de 1 a 6 átomos de carbono; alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con grupos halógeno, amino, o hidroxilo; o R^{11} y R^{12}, R^{12} y R^{15}, R^{15} y R^{16}, R^{13} y R^{14}, o R^{13} y R^{15}, junto con los átomos con los que están unidos, pueden formar un anillo de 3 a 7 miembros, saturado, insaturado, o parcialmente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O, y S, y opcionalmente sustituido con oxo y de 1 a 3 grupos R^5;

L es $(CR_2)_{1-4}$ o un enlace;

Y es un anillo carbocíclico de 3 a 7 átomos de carbono, arilo de 6 a 10 átomos de carbono, o un heteroarilo de 5 a 10 miembros o anillo heterocíclico de 4 a 10 miembros, cada uno de los cuales está

opcionalmente sustituido con 1 a 3 grupos R^5;

R^7, R^8 y R^{8a} son independientemente alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con halógeno, amino, hidroxilo o ciano; $(CR_2)_qY$ o alcoxilo de 1 a 6 átomos de carbono; o R^7 es H;

cada R es independientemente H o alquilo de 1 a 6 átomos de carbono;

R y R^7 junto con N en cada NRR^7 pueden formar un anillo de 5 a 6 miembros que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O, y S, y opcionalmente sustituido con oxo y de 1 a 3 grupos R^5;

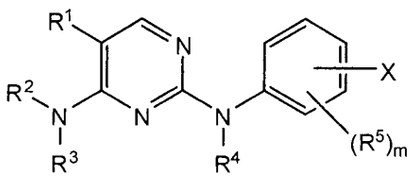
m es de 2 a 4;

n es de 1 a 3;

p es de 1 a 4; y

q es de 0 a 4.

En todavía otro aspecto, la invención proporciona los compuestos de la fórmula (5):



(1)

o las sales fisiológicamente aceptables de los mismos;

en donde X es un anillo heterocíclico de 4 a 7 miembros que contiene NR^6, $-\overset{O^-}{\underset{|}{N^+}}R^6$, O o S, y opcionalmente sustituido con 1 a 3

grupos R^5;

en donde R^1 es halógeno, alquilo de 1 a 6 átomos de carbono, o un alquilo de 1 a 6 átomos de carbono sustituido por halógeno;

R^2 es un heteroarilo de 5 a 6 miembros opcionalmente sustituido o un anillo heterocíclico de 5 a 7 miembros, cada uno teniendo de 1 a 3 heteroátomos seleccionados a partir de N, O y S y opcionalmente sustituido con 1 a 3 grupos R^9;

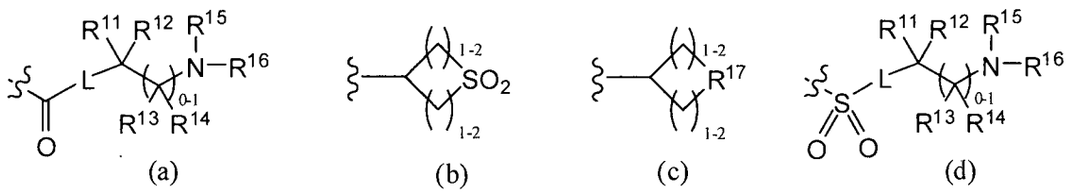
R^3 y R^4 son independientemente H, $C(O)R^8$, alquilo de 1 a 6 átomos de carbono, o alquilo de 1 a 6 átomos de carbono sustituido por halógeno;

R^5 y R^9 son independientemente alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con grupos halógeno, amino, o hidroxilo; o R^5 y R^9 son independientemente alcoxilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno, halógeno, nitro, ciano, $CR(OR^7)R^7$, OR^7, $O(CR_2)_p$-OR^7, $NR(R^7)$, $CR(R^7)NRR^7$, $(CR_2)_{1-6}NR(CR_2)_pOR^7$, $(CR_2)_{1-6}NR(CR_2)_qC(O)R^8$, $-C(O)-(CR_2)_q-NR-C(O)-R^8$, $(CR_2)_qY$, $C(O)O_{0-1}R^7$, $C(O)NR(R^7)$, $C(O)CRR^7$-$NR(R^7)$, $C(O)NR(CR_2)_pNR(R^7)$, $C(O)NR(CR_2)_pOR^7$, $C(O)NR(CR_2)_pSR^7$, $C(O)NR(CR_2)_pS(O)_{1-2}R^8$, $S(O)_{0-2}R^8$, $S(O)_2NRR^7$, $S(O)_2NR(CR_2)_pNR(R^7)$, o $S(O)_2NR(CR_2)_pOR^7$;

R^6 es H; alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con

halógeno, amino, hidroxilo o alcoxilo; $-(CR_2)_p-CN$; $C(O)H$; $CR(OR^7)R^7$, $(CR_2)_p-OR^7$, $(CR_2)_p-NR(R^7)$, $CR(R^7)NRR^7$, -L-Y, $-L-C(O)O_{0-1}-(CR_2)_q-R^8$, $-(CR_2)_p-C(O)O_{0-1}-R^7$, $-L-C(O)-NRR^7$, $-L-C(O)O_{0-1}-CR(R^7)-NRR^7$, $-L-C(O)-NR-(CR_2)_p-NRR^7$, $-L-C(O)NR(CR_2)_pOR^7$, $-L-C(O)-(CR_2)_q-NR-C(O)-R^8$, $-L-C(O)NR(CR_2)_pSR^7$, $-L-C(O)NR(CR_2)_pS(O)_{1-2}R^8$, $-L-S(O)_2R^8$, $(CR_2)_pNR(CR_2)_pOR^7$, $(CR_2)_pNR-L-C(O)R^8$, $-L-S(O)_2NRR^7$, $-L-S(O)_2NR(CR_2)_pNR(R^7)$ o $-L-S(O)_2NR(CR_2)_pOR^7$;

de una manera alternativa, R^6 es un radical seleccionado a partir de la fórmula (a), (b), (c) o (d):



en donde R^{11}, R^{12}, R^{13}, R^{14}, R^{15} y R^{16} se seleccionan independientemente a partir de H o alquilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con grupos halógeno, amino, o hidroxilo; o R^{11} y R^{12}, R^{12} y R^{15}, R^{15} y R^{16}, R^{13} y R^{14}, o R^{13} y R^{15} junto con los átomos de carbono y/o nitrógeno con los que están unidos, pueden formar un anillo de 3 a 7 miembros, saturado, insaturado, o parcialmente insaturado que opcionalmente contiene hasta 3 átomos o grupos seleccionados a partir de C(O), N, O y $S(O)_{0-2}$;

R^{17} es O o SO_2R^8;

L es $(CR_2)_{1-4}$ o un enlace;

Y es un anillo carbocíclico de 3 a 7 átomos de carbono, arilo de 6 a 10 átomos de carbono, o un heteroarilo de 5 a 10 miembros o anillo heterocíclico de 4 a 10 miembros, cada uno de los cuales está opcionalmente sustituido con 1 a 3 grupos R^5;

R^7 y R^8 son independientemente alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con halógeno, amino, hidroxilo o ciano; $(CR_2)_qY$ o alcoxilo de 1 a 6 átomos de carbono; o R^7 es H;

cada R es H o alquilo de 1 a 6 átomos de carbono;

m es de 2 a 4;

n es de 1 a 3;

p es de 1 a 4; y

q es de 0 a 4.

En la fórmula (5) anterior, en los ejemplos de heteroarilo de 5 a 6 miembros o de un anillo heterocíclico de 5 a 7 miembros, los grupos R^2 incluyen, pero no se limitan a, pirazolilo, pirrolilo, tiofenilo, pirimidinilo, isoxazolilo, piridilo, azepan-2-onilo, 2H-tiopirano, 3H-tiopirano, 4H-tiopirano, tetrahidro-tiopirano, 2H-pirano, 4H-pirano, tetrahidro-pirano, piperidina, 1,2-ditiina, 1,2-ditiano, 1,3-ditiina, 1,3-ditiano, 1,4-ditiina, 1,4-ditiano, 1,2- dioxina, 1,2-dioxano, 1,3-dioxina, 1,3-dioxano, 1,4-dioxina, 1,4-dioxano, piperazina, 1,2-oxatiina, 1,2-oxatiano, 4H-1,3-oxatiina, 1,3-oxatiano, 1,4-oxatiina, 1,4-oxatiano, 2H-1,2-tiazina, tetrahidro-1,2-tiazina, 2H-1,3-tiazina, 4H-1,3-tiazina,

5, 6-dihidro-4H-tiazina, 4H-1, 4-tiazina, tetrahidro-1, 4-tiazina, 2H-1,2-oxazina, 4H-1,2-oxazina, 6H-1,2-oxazina, 2H-1,3-oxazina, 4H-1,3-oxazina, 4H-1, 4-oxazina, morfolina, trioxano, 4H-1,2,3-tritiina, 1,2,3-tritiano, 1,3, 5-tritiano, hexahidro-1,3, 5-triazina, tetrahidro-tiofeno, tetrahidrofurano, pirrolina, pirrolidina, pirrolidona, pirrolidiona, pirazolina, pirazolidina, imidazolina, imidazolidina, 1,2-dioxol, 1,2-dioxolano, 1,3-dioxol, 1,3-dioxolano, 3H-1,2-ditiol, 1,2-ditiolano, 1,3-ditiol, 1,3-ditiolano, isoxazolina, isoxazolidina, oxazolina, oxazolidina, tiazolina, tiozolidina, 3H-1,2-oxatiol, 1,2-oxatiolano, 5H-1,2-oxatiol, 1,3-oxatiol, 1,3-oxatiolano, 1,2,3-tritiol, 1,2,3-tritiolano, 1,2, 4-tritiolano, 1,2,3-trioxol, 1,2,3-trioxolano, 1,2, 4-trioxolano, 1,2,3-triazolina, y 1,2,3-triazolidina.

En cada una de las fórmulas anteriores, cualesquiera átomos de carbono asimétricos pueden estar presentes en la configuración (R), (S), o (R,S). Los compuestos, por lo tanto, pueden estar presentes como mezclas de isómeros o como los isómeros puros, por ejemplo, como los enantiómeros o diaestereómeros puros. La invención abarca además los posibles tautómeros de los compuestos de la invención.

Cualquier fórmula dada en la presente también pretende representar las formas no marcadas así como las formas isotópicamente marcadas de los compuestos. Los compuestos isotópicamente marcados tienen las estructuras ilustradas por las fórmulas dadas en la presente, excepto que uno o más átomos son reemplazados por un átomo que tiene una masa atómica o número de

masa seleccionados. Los ejemplos de los isótopos que se pueden incorporar en los compuestos de la invención incluyen los isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, flúor, y cloro, tales como ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I respectivamente.

La invención incluye diferentes compuestos isotópicamente marcados como se definen en la presente, por ejemplo, aquéllos en donde están presentes los isótopos radioactivos, tales como ^{3}H, ^{13}C, y ^{14}C. Estos compuestos isotópicamente marcados son útiles en los estudios metabólicos (con, por ejemplo, ^{14}C), estudios de cinética de reacción (con, por ejemplo ^{2}H ó ^{3}H), técnicas de detección o de formación de imágenes, tales como tomografía por emisión de positrones (PET) o tomografía computarizada con emisión de un solo fotón (SPECT), incluyendo ensayos de distribución del fármaco o del sustrato en el tejido, o en el tratamiento radioactivo de los pacientes. En otros ejemplos, se puede utilizar un ^{18}F o compuesto marcado para los estudios de PET o SPECT. Las variaciones isotópicas de los compuestos tienen el potencial para cambiar el destino metabólico de un compuesto y/o para crear pequeños cambios en las propiedades físicas, tales como la hidrofobicidad, y similares. Las variaciones isotópicas también tienen el potencial para mejorar la eficacia y la seguridad, para mejorar la bidisponibilidad y la vida media, para alterar el enlace de proteína, para cambiar la biodistribución, para aumentar la proporción de metabolitos activos, y/o para disminuir la formación de metabolitos reactivos o tóxicos.

Los compuestos isotópicamente marcados de esta invención y los pro-fármacos de los mismos se pueden preparar en términos generales llevando a cabo los procedimientos que se dan a conocer en los esquemas o en los Ejemplos y preparaciones que se describen más adelante, mediante la utilización de un reactivo isotópicamente marcado fácilmente disponible para sustituir a un reactivo no isotópicamente marcado.

En cada una de las fórmulas anteriores, cada fracción opcionalmente sustituida puede estar sustituida con alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 3 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente halogenado, o puede tener opcionalmente un átomo de carbono que puede ser reemplazado o sustituido con N, S, O, o una combinación de los mismos (por ejemplo, hidroxi-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono); halógeno, amino, amidino, alcoxilo de 1 a 6 átomos de carbono; hidroxilo, metilendioxilo, carboxilo; alquilo de 1 a 8 átomos de carbono-carbonilo, alcoxilo de 1 a 8 átomos de carbono-carbonilo, carbamoílo, alquilo de 1 a 8 átomos de carbono-carbamoílo, sulfamoílo, ciano, oxo, nitro, o un anillo carbocíclico, anillo heterocíclico, arilo, o heteroarilo opcionalmente sustituidos, como se describen anteriormente.

Farmacología y Utilidad

Los compuestos de la invención y sus sales farmacéuticamente aceptables exhiben valiosas propiedades farmacológicas cuando se

prueban *in vitro* en ensayos de cinasa sin células y en ensayos celulares, y, por consiguiente, son útiles como productos farmacéuticos.

En un aspecto, los compuestos de la invención pueden inhibir el receptor del factor de crecimiento tipo insulina I (IGF-1R), y pueden ser útiles en el tratamiento de las enfermedades mediadas por el IGF-1R. Los ejemplos de las enfermedades mediadas por el IGF-1R incluyen, pero no se limitan a, enfermedades proliferativas, tales como tumores, por ejemplo de mama, renal, de próstata, colo-rectal, de tiroides, de ovarios, de páncreas, neuronales, de pulmón, uterino, y tumores gastrointestinales, así como osteosarcomas y melanomas. La eficacia de los compuestos de la invención como inhibidores de la actividad de cinasa de tirosina del IGF-1R se puede demostrar utilizando un ELISA de captura celular. En este ensayo, se determina la actividad de los compuestos de la invención contra la auto-fosforilación inducida por (IGF-1) del IGF-1R.

En otro aspecto, los compuestos de la invención pueden inhibir la actividad de cinasa de tirosina de la cinasa de linfoma anaplásico (ALK), y la proteína de fusión de NPM-ALK. Esta cinasa de proteína tirosina resulta a partir de una fusión genética de nucleofosmina (NPM) y ALK, que hace que la actividad de cinasa de proteína tirosina del ligando de ALK sea independiente. NPM-ALK tiene un papel clave en la transmisión de señales en un número de células hematopoiéticas y otras células humanas que conducen a enfermedades hematológicas y neoplásicas, por ejemplo en el

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linfoma macrocelular anaplásico (ALCL), y en los linfomas no de Hodgkin (NHL), específicamente en ALK+NHL o Alkomas, en los tumores miofibroblásticos inflamatorios (IMT), y en los neuroblastomas. (Duyster y colaboradores, 2001 Oncogene 20, 5623-5637). En adición a NPM-ALK, se han identificado otras fusiones genéticas en las enfermedades hematológicas y neoplásicas humanas; por ejemplo, TPM3-ALK (una fusión de tropomiosina no muscular con ALK).

La inhibición de la actividad de cinasa de tirosina de ALK se puede demostrar empleando los métodos conocidos, por ejemplo utilizando el dominio de cinasa recombinante de ALK en analogía al ensayo de cinasa VEGF-R descrito en J. Wood y colaboradores, Cancer Res. 60, 2178-2189 (2000). En general, se llevan a cabo ensayos enzimáticos *in vitro* utilizando cinasa de proteína tirosina GST-ALK, en placas de 96 pozos, como un ensayo de enlace de filtro en Tris HCl 20 mM, pH = 7.5, $MgCl_2$ 3 mM, $MnCl_2$ 10 mM, DTT 1 mM, 0.1 µCi/ensayo (= 30 microlitros) [γ-^{33}P]-ATP, ATP 2 µM, 3 microgramos/mililitro de poli-(Glu, Tyr 4:1) Poly-EY (Sigma P-0275), sulfóxido de dimetilo al 1 por ciento, y 25 nanogramos de enzima ALK. Los ensayos se incuban durante 10 minutos a temperatura ambiente. Las reacciones se terminan mediante la adición de 50 microlitros de EDTA 125 mM, y la mezcla de reacción se transfiere a una placa MAIP Multiscreen (Millipore, Bedford, MA, EUA), previamente humedecida con metanol, y se rehidrata durante 5 minutos con H_2O. En seguida del lavado (H_3PO_4 al 0.5 por ciento),

las placas se cuentan en un contador de cintilación de líquidos. Los valores IC_{50} se calculan mediante análisis de regresión lineal del porcentaje de inhibición.

Los compuestos de la invención pueden inhibir potentemente el crecimiento de las células BaF3 de murino que sobre-expresan la NPM-ALK humana (DSMZ Deutsche Sammiung von Mikroorganismen und Zelikulturen GmbH, Alemania). La expresión de NPM-ALK se puede lograr mediante la transfección de la línea celular BaF3 con un vector de expresión pCIneo^{MR} (Promega Corp., Madison WI, EUA) que codifica para NPM-ALK, y la subsiguiente selección de las células resistentes a G418. Las células BaF3 no transfectadas dependen de la IL-3 para la sobrevivencia celular. En contraste, las células BaF3 que expresan NPM-ALK (denominadas como BaF3-NPM-ALK posteriormente en la presente) pueden proliferar en ausencia de IL-3, debido a que obtienen la señal proliferativa a través de la cinasa NPM-ALK. Por consiguiente, los inhibidores supuestos de la cinasa NPM-ALK eliminan la señal de crecimiento, y pueden dar como resultado una actividad anti-proliferativa. La actividad anti-proliferativa de los inhibidores supuestos de la cinasa NPM-ALK, sin embargo, se puede superar mediante la adición de IL-3, la cual proporciona señales de crecimiento a través de un mecanismo independiente de NPM-ALK. También se ha descrito un sistema celular análogo que utiliza la cinasa FLT3 (véase, E Weisberg y colaboradores, Cancer Cell; 1, 433-443 (2002)).

La actividad inhibidora de los compuestos de la invención se

puede determinar como sigue. En general, las células BaF3-NPM-ALK (15,000/pozo de placa de microtitulación) se transfieren a placas de microtitulación de 96 pozos. Los compuestos de prueba disueltos en sulfóxido de dimetilo (DMSO) se agregan en una serie de concentraciones (serie de dilución), de tal manera que la concentración final de sulfóxido de dimetilo no sea mayor del 1 por ciento (volumen/volumen). Después de la adición, las placas se incuban durante dos días, durante lo cual, los cultivos de control sin compuesto de prueba son capaces de sufrir dos ciclos de división celular. El crecimiento de las células BaF3-NPM-ALK se mide por medio del teñido YOPRO^{MR} [T Idziorek y colaboradores, J. Immunol. Methods; 185: 249-258 (1995)]: A cada pozo se le agregan 25 microlitros de regulador de lisis que comprende citrato de sodio 20 mM, pH de 4.0, cloruro de sodio 26.8 mM, NP40 al 0.4 por ciento, y EDTA 20 mM a cada pozo. La lisis celular se completa dentro de 60 minutos a temperatura ambiente, y se determina la cantidad total de YOPRO^{MR} enlazado al ADN, mediante una medición que utiliza el lector de 96 pozos Cytofluor II (PerSeptive Biosystems) con las siguientes posiciones: Excitación (nanómetros) 485/20 y Emisión (nanómetros) 530/25.

Los compuestos de la invención también pueden ser útiles en el tratamiento y/o la prevención de enfermedades o trastornos inflamatorios agudos o crónicos, o enfermedades autoinmunes, por ejemplo, artritis reumatoide, osteoartritis, lupus eritematoso sistémico, tiroiditis de Hashimoto, esclerosis múltiple, miastenia

gravis, diabetes (tipos I y II) y los trastornos asociados con la misma, enfermedades respiratorias, tales como asma o lesión inflamatoria del hígado, lesión inflamatoria glomerular, manifestaciones cutáneas de trastornos o enfermedades inmunológicamente mediadas, enfermedades inflamatorias e híper-proliferativas de la piel (tales como soriasis, dermatitis atópica, dermatitis alérgica por contacto, dermatitis por contacto irritante y otras dermatitis eczematosas, dermatitis seborreica), enfermedades inflamatorias de los ojos, por ejemplo, síndrome de Sjoegren, queratoconjuntivitis o uveítis, enfermedad inflamatoria del intestino, enfermedad de Crohn, o colitis ulcerativa.

De acuerdo con lo anterior, la presente invención proporciona:

(1) un compuesto de la invención para utilizarse como un producto farmacéutico;

(2) un compuesto de la invención para utilizarse como un inhibidor de IGF-1R, por ejemplo para utilizarse en cualquiera de las indicaciones particulares estipuladas anteriormente en la presente;

(3) una composición farmacéutica, por ejemplo, para utilizarse en cualquiera de las indicaciones estipuladas anteriormente en la presente, la cual comprende un compuesto de la invención como ingrediente activo, junto con uno o más diluyentes o vehículos farmacéuticamente aceptables;

(4) un método para el tratamiento de cualquier indicación particular estipulada anteriormente en la presente, en un sujeto que lo necesite, el cual comprende administrar una cantidad efectiva de

un compuesto de la invención o una composición farmacéutica que lo comprenda;

(5) el uso de un compuesto de la invención para la fabricación de un medicamento para el tratamiento o la prevención de una enfermedad o condición, en donde tiene un papel o está implicada la activación de IGF-1R;

(6) el método como se define anteriormente bajo (4), el cual comprende la co-administración, por ejemplo, de una manera concomitante o en secuencia, de una cantidad terapéuticamente efectiva de un compuesto de la invención, y una o más sustancias de fármaco adicionales, siendo esta sustancia de fármaco adicional útil en cualquiera de las indicaciones particulares estipuladas anteriormente en la presente;

(7) una combinación que comprende una cantidad terapéuticamente efectiva de un compuesto de la invención, y una o más sustancias de fármaco adicionales, siendo esta sustancia de fármaco adicional útil en cualquiera de las indicaciones particulares estipuladas anteriormente en la presente;

(8) el uso de un compuesto de la invención para la fabricación de un medicamento para el tratamiento o la prevención de una enfermedad que responda a la inhibición de la cinasa de linfoma anaplásico;

(9) el uso de acuerdo con (8), en donde la enfermedad que se va a tratar se selecciona a partir de linfoma macrocelular anaplásico, linfomas no de Hodgkin, tumores miofibroblásticos

inflamatorios, neuroblastomas, y enfermedades neoplásicas;

(10) el uso de acuerdo con (8) o (9), en donde el compuesto es cualquiera de los ejemplos, o una sal farmacéuticamente aceptable de los mismos;

(11) un método para el tratamiento de una enfermedad que responda a la inhibición de la cinasa de linfoma anaplásico, en especial una enfermedad seleccionada de linfoma macrocelular anaplásico, linfomas no de Hodgkin, tumores miofibroblásticos inflamatorios, neuroblastomas, y enfermedades neoplásicas, el cual comprende administrar una cantidad efectiva de un compuesto de la invención o una sal farmacéuticamente aceptable del mismo.

Administración y Composiciones Farmacéuticas

En general, los compuestos de la invención se administrarán en cantidades terapéuticamente efectivas por medio de cualquiera de los modos usuales y aceptables conocidos en la materia, ya sea de una manera individual o bien en combinación con uno o más agentes terapéuticos. Una cantidad terapéuticamente efectiva puede variar ampliamente dependiendo de la gravedad de la enfermedad, de la edad y salud relativa del sujeto, de la potencia del compuesto utilizado, y de otros factores conocidos por aquéllos de una experiencia ordinaria en este campo. Por ejemplo, para el tratamiento de enfermedades neoplásicas y trastornos del sistema inmunológico, la dosificación requerida también variará dependiendo del modo de administración, de la condición particular que se vaya a tratar, y del efecto deseado.

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En general, se indica que se obtienen resultados satisfactorios sistémicamente en dosificaciones diarias de aproximadamente 0.01 a aproximadamente 100 miligramos/kilogramo de peso corporal, o en particular, de aproximadamente 0.03 a 2.5 miligramos/kilogramo de peso corporal. Una dosificación diaria indicada en el mamífero superior, por ejemplo, en los seres humanos, puede estar en el intervalo de aproximadamente 0.5 miligramos a aproximadamente 2,000 miligramos, o más particularmente, de aproximadamente 0.5 miligramos a aproximadamente 100 miligramos, convenientemente administrados, por ejemplo, en dosis divididas hasta cuatro veces al día o en una forma retardada. Las formas de dosificación unitaria adecuadas para su administración oral comprenden de aproximadamente 1 a 50 miligramos de ingrediente activo.

Los compuestos de la invención se pueden administrar como composiciones farmacéuticas por cualquier vía convencional; por ejemplo, enteralmente, por ejemplo, oralmente, por ejemplo, en la forma de tabletas o cápsulas; parenteralmente, por ejemplo, en la forma de soluciones o suspensiones inyectables; o tópicamente, por ejemplo, en la forma de lociones, geles, ungüentos o cremas, o en una forma nasal o de supositorio.

Las composiciones farmacéuticas que comprenden un compuesto de la presente invención en forma libre o en forma de sal farmacéuticamente aceptable, en asociación con cuando menos un vehículo o diluyente farmacéuticamente aceptable, se puede fabricar de una manera convencional mediante los procesos de mezcla,

granulación, recubrimiento, disolución, o liofilización. Por ejemplo, las composiciones farmacéuticas que comprenden un compuesto de la invención en asociación con cuando menos un vehículo o diluyente farmacéuticamente aceptable, se pueden fabricar de una manera convencional mezclando con un vehículo o diluyente farmacéuticamente aceptable. Las formas de dosificación unitaria para su administración oral contienen, por ejemplo, de aproximadamente 0.1 miligramos a aproximadamente 500 miligramos de sustancia activa.

En una modalidad, las composiciones farmacéuticas son soluciones del ingrediente activo, incluyendo suspensiones o dispersiones, tales como soluciones acuosas isotónicas. En el caso de las composiciones liofilizadas que comprenden al ingrediente activo solo o junto con un vehículo tal como manitol, las dispersiones o suspensiones se pueden formar antes de usarse. Las composiciones farmacéuticas se pueden esterilizar y/o pueden contener adyuvantes, tales como agentes conservadores, estabilizantes, humectantes o emulsionantes, promotores de solución, sales para regular la presión osmótica y/o reguladores del pH. Los conservadores adecuados incluyen, pero no se limitan a, antioxidantes tales como ácido ascórbico, o microbicidas, tales como ácido sórbico o ácido benzoico. Las soluciones o suspensiones pueden comprender agentes incrementadores de viscosidad, incluyendo, pero no limitándose a, carboxi-metil-celulosa de sodio, carboxi-metil-celulosa, dextrano, polivinil-pirrolidona, gelatinas, o

solubilizantes, por ejemplo, Tween 80 (mono-oleato de sorbitán de polioxietileno (20)).

Las suspensiones en aceite pueden comprender, como el componente de aceite, los aceites vegetales, sintéticos, o semi-sintéticos acostumbrados para propósitos de inyección. Los ejemplos incluyen ésteres de ácidos grasos líquidos que contienen, como el componente de ácido, un ácido graso de cadena larga que tiene de 8 a 22 átomos de carbono, o en algunas modalidades, de 12 a 22 átomos de carbono. Los ésteres de ácidos grasos líquidos adecuados incluyen, pero no se limitan a, ácido láurico, ácido tridecílico, ácido mirístico, ácido pentadecílico, ácido palmítico, ácido margárico, ácido esteárico, ácidó araquídico, ácido behénico, o los ácidos insaturados correspondientes, por ejemplo ácido oleico, ácido elaídico, ácido erúcico, ácido brasídico, y ácido linoleico, y, si se desea, pueden contener antioxidantes, por ejemplo vitamina E, 3-caroteno, ó 3,5-diterbutil-hidroxi-tolueno. El componente de alcohol de estos ésteres de ácidos grasos puede tener seis átomos de carbono, y puede ser monovalente o polivalente, por ejemplo un alcohol mono-, di-, o tri-valente. Los componentes de alcohol adecuados incluyen, pero no se limitan a, metanol, etanol, propanol, butanol o pentanol, o isómeros de los mismos; glicol y glicerol.

Otros ésteres de ácidos grasos adecuados incluyen, pero no se limitan a, oleato de etilo, miristato de isopropilo, palmitato de isopropilo, LABRAFIL® M 2375, (polioxietilen-glicerol), LABRAFIL® M 1944 CS (glicéridos poliglicolizados insaturados preparados

mediante la alcohólisis del aceite de semilla de chabacano y que comprenden glicéridos y éster de polietilenglicol), LABRASOL^{MR} (glicéridos poliglicolizados saturados preparados mediante la alcohólisis de TCM, y que comprenden glicéridos y éster de polietilenglicol; todos disponibles en Gatefossé, Francia), y/o MIGLYOL® 812 (triglicérido de ácidos grasos saturados de una longitud de cadena de 8 a 12 átomos de carbono, de Hüls AG, Alemania), y aceites vegetales, tales como aceite de semilla de algodón, aceite de almendra, aceite de oliva, aceite de ricino, aceite de ajonjolí, aceite de semilla de soya, o aceite de cacahuate.

Las composiciones farmacéuticas para su administración oral se pueden obtener, por ejemplo, mediante la combinación del ingrediente activo con uno o más vehículos sólidos, y si se desea, se granula una mezcla resultante, y se procesa la mezcla o los gránulos mediante la inclusión de excipientes adicionales, para formar tabletas o núcleos de tabletas.

Los vehículos adecuados incluyen, pero no se limitan a, rellenos, tales como azúcares, por ejemplo lactosa, sacarosa, manitol o sorbitol, preparaciones de celulosa, y/o fosfatos de calcio, por ejemplo trifosfato de calcio o fosfato ácido de calcio, y también aglutinantes, tales como almidones, por ejemplo almidón de maíz, de trigo, de arroz, o de papa, metil-celulosa, hidroxi-propil-metil-celulosa, carboxi-metil-celulosa de sodio, y/o polivinil-pirrolidona, y/o, si se desea, desintegrantes, tales como los almidones anteriormente mencionados, almidón de carboxi-metilo, polivinil-

pirrolidona reticulada, ácido algínico o una sal del mismo, tal como alginato de sodio. Los excipientes adicionales incluyen acondicionadores de flujo y lubricantes, por ejemplo ácido silícico, talco, ácido esteárico o sales del mismos, tal como estearato de magnesio o de calcio, y/o polietilenglicol, o derivados de los mismos.

Los núcleos de tabletas pueden ser provistas con recubrimientos adecuados, opcionalmente entéricos, a través del uso de, entre otras cosas, soluciones concentradas de azúcar, las cuales pueden comprender goma arábiga, talco, polivinil-pirrolidona, polietilenglicol y/o dióxido de titanio, o soluciones de recubrimiento en los solventes o mezclas de solventes orgánicos adecuados, o, para la preparación de los recubrimientos entéricos, soluciones de preparaciones de celulosa adecuadas, tales como ftalato de acetil-celulosa o ftalato de hidroxi-propil-metil-celulosa. Se pueden agregar tintes o pigmentos a las tabletas o recubrimientos de tabletas, por ejemplo, para propósitos de identificación, o para indicar diferentes dosis del ingrediente activo.

Las composiciones farmacéuticas para su administración oral también pueden incluir cápsulas duras, las cuales comprenden gelatina, o cápsulas selladas blandas, las cuales comprenden gelatina y un plastificante, tal como glicerol o sorbitol. Las cápsulas duras pueden contener al ingrediente activo en la forma de gránulos, por ejemplo en mezcla con rellenos, tales como almidón de maíz, aglutinantes, y/o derrapantes, tales como talco o estearato de magnesio, y opcionalmente estabilizantes. En las cápsulas blandas,

el ingrediente activo se puede disolver o suspender en excipientes líquidos adecuados, tales como aceites grasos, aceite de parafina, o polietilenglicoles líquidos, o ésteres de ácidos grasos de etilen- o propilen-glicol, a los cuales también se les pueden agregar estabilizantes y detergentes, por ejemplo, del tipo de éster de ácido graso de sorbitán de polioxietileno.

Las composiciones farmacéuticas adecuadas para administración rectal son, por ejemplo, supositorios, los cuales comprenden una combinación del ingrediente activo y una base para supositorios. Las bases para supositorios adecuadas son, por ejemplo, triglicéridos naturales o sintéticos, hidrocarburos de parafina, polietilenglicoles, o alcanoles superiores.

Las composiciones farmacéuticas adecuadas para su administración parenteral pueden comprender soluciones acuosas de un ingrediente activo en una forma soluble en agua, por ejemplo de una sal soluble en agua, o suspensiones acuosas para inyección que contienen sustancias incrementadoras de viscosidad, por ejemplo carboxi-metil-celulosa de sodio, sorbitol y/o dextrano, y, si se desea, estabilizantes. El ingrediente activo, opcionalmente junto con excipientes, también puede estar en la forma de un liofilizado, y se puede hacer en una solución antes de su administración parenteral mediante la adición de solventes adecuados. Las soluciones, tales como se utilizan, por ejemplo, para su administración parenteral, también se pueden emplear como soluciones para infusión. La fabricación de preparaciones inyectables usualmente se lleva a cabo

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bajo condiciones estériles, así como el llenado, por ejemplo, en ampolletas o frascos, y el sellado de los recipientes.

Los compuestos de la invención se pueden administrar como el único ingrediente activo, o junto con otros fármacos útiles contra las enfermedades neoplásicas o útiles en regímenes inmuno-moduladores. Por ejemplo, los compuestos de la invención se pueden utilizar de acuerdo con la invención en combinación con composiciones farmacéuticas efectivas en diferentes enfermedades como se describe anteriormente, por ejemplo, con ciclofosfamida, 5-fluoro-uracilo, fludarabina, gemcitabina, cisplatino, carboplatina, vincristina, vinblastina, etoposida, irinotecano, paclitaxel, docetaxel, rituxan, doxorrubicina, gefitinib, o imatinib; o también con ciclosporinas, rapamicinas, ascomicinas o sus análogos inmuno-supresores, por ejemplo, ciclosporina A, ciclosporina G, FK-506, sirolimus o everolimus, corticosteroides, por ejemplo, prednisona, ciclofosfamida, azatiopreno, metotrexato, sales de oro, sulfasalazina, anti-malaria, brequinar, leflunomida, mizoribina, ácido micofenólico, micofenolato-mofetil, 15-desoxi-espergualina, anticuerpos monoclonales inmuno-supresores, por ejemplo, anticuerpos monoclonales para los receptores de leucocitos, por ejemplo, MHC, CD2, CD3, CD4, CD7, CD25, CD28, I CD40, CD45, CD58, CD80, CD86, CD152, CD137, CD154, ICOS, LFA-1, VLA-4 o sus ligandos, u otros compuestos inmuno-moduladores, por ejemplo, CTLA41g.

La invención también proporciona combinaciones farmacéuticas, por ejemplo, un kit, el cual comprende: a) un primer

agente, el cual es un compuesto de la invención como se da a conocer en la presente, en forma libre o en forma de sal farmacéuticamente aceptable, y b) cuando menos un co-agente. El kit puede comprender instrucciones para su administración.

Procesos para la Elaboración de los Compuestos de la Invención

Los Procedimientos Generales para la preparación de los compuestos de la invención se describen en los Ejemplos que se encuentran más adelante. En las reacciones descritas, los grupos funcionales reactivos, por ejemplo los grupos hidroxilo, amino, imino, tio, o carboxilo, en donde se deseen éstos en el producto final, se pueden proteger para evitar su participación indeseada en las reacciones. Se pueden utilizar los grupos protectores convencionales de acuerdo con la práctica estándar (véase, por ejemplo, T.W. Greene y P. G. M. Wuts en "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991).

Los compuestos de la invención, incluyendo sus sales, también se pueden obtener en la forma de hidratos, o sus cristales pueden incluir, por ejemplo, al solvente utilizado para la cristalización (presentes como solvatos). Las sales usualmente se pueden convertir hasta los compuestos en forma libre, por ejemplo, mediante el tratamiento con agentes básicos adecuados, por ejemplo con carbonatos de metales alcalinos, carbonatos ácidos de metales alcalinos, o hidróxidos de metales alcalinos, tales como carbonato de potasio o hidróxido de sodio. Un compuesto de la invención en una forma de sal de adición de base se puede convertir hasta el ácido

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libre correspondiente mediante el tratamiento con un ácido adecuado (por ejemplo, ácido clorhídrico, etc.). En vista de la estrecha relación entre los compuestos novedosos en forma libre y aquéllos en la forma de sus sales, incluyendo las sales que se pueden utilizar como intermediarios, por ejemplo en la purificación o identificación de los compuestos novedosos, cualquier referencia a los compuestos libres anteriormente en la presente y posteriormente en la presente, se debe entender para referirse también a las sales correspondientes, como sea apropiado.

Las sales de los compuestos de la invención con un grupo formador de sal se pueden preparar de una manera conocida por sí misma. Las sales de adición de ácido de los compuestos de la fórmula (1), (2), (3), y (4), por consiguiente, se pueden obtener mediante el tratamiento con un ácido o con un reactivo de intercambio de aniones adecuado. Las sales farmacéuticamente aceptables de los compuestos de la invención se pueden formar, por ejemplo, como las sales de adición de ácido, con ácidos orgánicos o inorgánicos, a partir de los compuestos de la fórmula (1), (2), (3), y (4) con un átomo de nitrógeno básico.

Los ácidos inorgánicos adecuados incluyen, pero no se limitan a, ácidos de halógeno, tales como ácido clorhídrico, ácido sulfúrico, o ácido fosfórico. Los ácidos orgánicos adecuados incluyen, pero no se limitan a, los ácidos carboxílicos, fosfóricos, sulfónicos o sulfámicos, por ejemplo ácido acético, ácido propiónico, ácido octanoico, ácido decanoico, ácido dodecanoico, ácido glicólico, ácido

láctico, ácido fumárico, ácido succínico, ácido adípico, ácido pimélico, ácido subérico, ácido azelaico, ácido málico, ácido tartárico, ácido cítrico, aminoácidos, tales como ácido glutámico o ácido aspártico, ácido maleico, ácido hidroxi-maleico, ácido metil-maleico, ácido ciclohexan-carboxílico, ácido adamantan-carboxílico, ácido benzoico, ácido salicílico, ácido 4-amino-salicílico, ácido ftálico, ácido fenil-acético, ácido mandélico, ácido cinámico, ácido metan- o etan-sulfónico, ácido 2-hidroxi-etan-sulfónico, ácido etan-1,2-disulfónico, ácido bencen-sulfónico, ácido 2-naftalen-sulfónico, ácido 1,5-naftalen-disulfónico, ácido 2-, 3-, ó 4 metil-bencen-sulfónico, ácido metil-sulfúrico, ácido etil-sulfúrico, ácido dodecil-sulfúrico, ácido N-ciclohexil-sulfámico, ácido N-metil-, N-etil-, o N-propil-sulfámico, u otros ácidos protónicos orgánicos, tales como ácido ascórbico.

Para los propósitos de aislamiento o purificación, también es posible utilizar sales farmacéuticamente inaceptables, por ejemplo picratos o percloratos. Para uso terapéutico, solamente se emplean las sales farmacéuticamente aceptables o los compuestos libres (donde sea aplicable, en la forma de preparaciones farmacéuticas).

Los compuestos de la invención en una forma no oxidada, se pueden preparar a partir de N-óxidos de los compuestos de la invención mediante el tratamiento con un agente reductor (por ejemplo, azufre, dióxido de azufre, trifenil-fosfina, borohidruro de litio, borohidruro de sodio, tricloruro de fósforo, tribromuro, o similares) en un solvente orgánico inerte adecuado (por ejemplo,

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acetonitrilo, etanol, dioxano acuoso, o similares) de 0°C a 80°C.

Los derivados de pro-fármaco de los compuestos de la invención se pueden preparar mediante los métodos conocidos por aquéllos de una experiencia ordinaria en la materia (por ejemplo, para mayores detalles, véase Saulnier y colaboradores, (1994), Bioorganic and Medicinal Chemistry Letters, Volumen 4, página 1985). Por ejemplo, los pro-fármacos apropiados se pueden preparar mediante la reacción de un compuesto no derivado de la invención con un agente carbamilante adecuado (por ejemplo, 1,1-aciloxi-alquil-carbano-cloridato, carbonato de *para*-nitro-fenilo, o similares).

Los derivados protegidos de los compuestos de la invención se pueden hacer por medios conocidos por aquéllos de una experiencia ordinaria en este campo. Se puede encontrar una descripción detallada de las técnicas aplicables a la creación de los grupos protectores y su remoción en T. W. Greene, "Protecting Groups in Organic Chemistry", 3ª Edición, John Wiley and Sons, Inc., 1999.

Los compuestos de la invención se pueden preparar como sus estereoisómeros individuales mediante la reacción de una mezcla racémica del compuesto con un agente de resolución ópticamente activo para formar un par de compuestos diaestereoisoméricos, se separan los diaestereómeros, y se recuperan los enantiómeros ópticamente puros. La resolución de los enantiómeros se puede llevar a cabo utilizando derivados diaestereoméricos covalentes de los compuestos de la invención, o mediante la utilización de complejos disociables (por ejemplo, sales diaestereoméricas

cristalinas). Los diaestereómeros tienen distintas propiedades físicas (por ejemplo, puntos de fusión, puntos de ebullición, solubilidades, reactividad, etc.), y se pueden separar fácilmente aprovechando estas diferencias. Los diaestereómeros se pueden separar mediante cristalización fraccionaria, cromatografía, o mediante técnicas de separación / resolución, basándose en las diferencias en la solubilidad. Entonces se recupera el enantiómero ópticamente puro, junto con el agente de resolución, por cualquier medio práctico que no dé como resultado la racemización. Se puede encontrar una descripción más detallada de las técnicas aplicables a la resolución de estereoisómeros de los compuestos a partir de su mezcla racémica en Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley and Sons, Inc., 1981.

En resumen, los compuestos de la invención se pueden hacer mediante un proceso como se describe en los Ejemplos; y

(a) opcionalmente convertir un compuesto de la invención en una sal farmacéuticamente aceptable;

(b) opcionalmente convertir una forma de sal de un compuesto de la invención hasta una forma no de sal;

(c) opcionalmente convertir una forma no oxidada de un compuesto de la invención hasta un N-óxido farmacéuticamente aceptable;

(d) opcionalmente convertir una forma de N-óxido de un compuesto de la invención hasta su forma no oxidada;

(e) opcionalmente resolver un isómero individual de un compuesto de la invención a partir de una mezcla de isómeros;

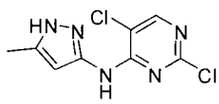
(f) opcionalmente convertir un compuesto no derivado de la invención hasta un derivado de pro-fármaco farmacéuticamente aceptable; y

(g) opcionalmente convertir un derivado de pro-fármaco de un compuesto de la invención hasta su forma no derivada.

Hasta donde no se describa particularmente la producción de los materiales de partida, los compuestos son conocidos o se pueden preparar de una manera análoga a los métodos conocidos en la técnica, o como se da a conocer en los Ejemplos posteriormente en la presente. Un experto en la materia apreciará que las transformaciones anteriores son solamente representativas de los métodos para la preparación de los compuestos de la presente invención, y que se pueden emplear similarmente otros métodos bien conocidos. La presente invención se ejemplifica además, pero no se limita, mediante los siguientes Ejemplos que ilustran la preparación de los compuestos de la invención.

Intermediario 1

2,5-dicloro-N-(5-metil-1H-pirazol-3-il)-pirimidin-4-amina

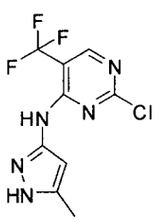


Una mezcla de 5-metil-1H-pirazol-3-amina (3.00 gramos, 30.9 milimoles), 2,4,5-tricloro-pirimidina (5.67 gramos, 30.9 milimoles, 1 equivalente), y Na_2CO_3 (3.60 gramos, 34.0 milimoles, 1.1

equivalentes) en EtOH (100 mililitros) se calentó a 40°C durante 24 horas. El solvente se removió al vacío. El residuo resultante se dividió entre EtOAc (350 mililitros), y agua (100 mililitros). La capa de EtOAc se lavó con agua (3 veces), NaCl acuoso saturado (1 vez), y se secó sobre Na_2SO_4. La solución de EtOAc resultante se concentró al vacío, proporcionando el producto de 2,5-dicloro-N-(5-metil-1H-pirazol-3-il)-pirimidin-4-amina; ESMS *m/z* 244.0 ($M + H^+$).

Intermediario 2

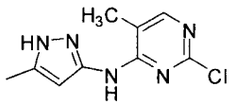
2-cloro-N-(5-metil-1H-pirazol-3-il)-5-(trifluoro-metil)-pirimidin-4-amina



Una mezcla de 2,4-dicloro-5-(trifluoro-metil)-pirimidina (1.06 gramos, 4.86 milimoles), 5-metil-1H-pirazol-3-amina (472.2 miligramos, 4.86 milimoles), y carbonato de sodio (2.06 gramos, 19.4 milimoles) en 100 mililitros de EtOH, se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró al vacío. El sólido crudo se dividió entre EtOAc y agua. Los extractos orgánicos combinados se secaron (Na_2SO_4), se concentraron al vacío, y se purificaron mediante cromatografía en sílice (EtOAc/ hexanos: 1/1), para proporcionar la 2-cloro-N-(5-metil-1H-pirazol-3-il)-5-(trifluoro-metil)-pirimidin-4-amina; ESMS *m/z* 278.0 ($M + H^+$).

Intermediario 3

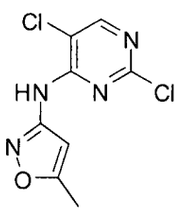
2-cloro-5-metil-N-(5-metil-1H-pirazol-3-il)-pirimidin-4-amina



Una mezcla de 5-metil-1H-pirazol-3-amina (3.00 gramos, 30.9 milimoles), 2,4-dicloro-5-metil-pirimidina (5.03 gramos, 30.9 milimoles, 1 equivalente), y Na_2CO_3 (3.60 gramos, 34.0 milimoles, 1.1 equivalentes) en EtOH (100 mililitros) se calentó a 40°C durante 24 horas. El solvente se removió al vacío. El residuo resultante se dividió entre EtOAc (350 mililitros), y agua (100 mililitros). La capa de EtOAc se lavó con agua (3 veces), NaCl acuoso saturado (1 vez), se secó sobre Na_2SO_4, y se concentró al vacío. El producto crudo resultante se sonicó en Et_2O (200 mililitros), y el precipitado resultante se recolectó mediante filtración. Este polvo se lavó adicionalmente con Et_2O, proporcionando el producto de 2-cloro-5-metil-N-(5-metil-1H-pirazol-3-il)-pirimidin-4-amina; ESMS *m/z* 224.1 ($M + H^+$).

Intermediario 4

N-(2,5-dicloro-pirimidin-4-il)-5-metil-isoxazol-3-amina

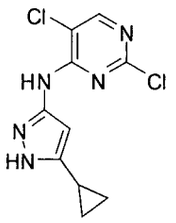


La mezcla de 5-metil-isoxazol-3-amina (98 miligramos, 1.0 milimoles), 2,4,5-tricloro-pirimidina (344 microlitros, 3.0 milimoles), y carbonato de sodio (106 miligramos, 1.0 milimoles) en 3 mililitros de EtOH se calentó a 60°C durante la noche. La mezcla de reacción se

concentró y entonces se dividió entre EtOAc y salmuera. Los extractos orgánicos recolectados se secaron (Na_2SO_4), se concentraron al vacío, y se purificaron mediante cromatografía en gel de sílice (MeOH/DCM: 1/9), para proporcionar la N-(2,5-dicloro-pirimidin-4-il)-5-metil-isoxazol-3-amina; ESMS *m/z* 245.0 ($M + H^+$).

Intermediario 5

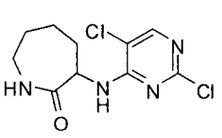
2,5-dicloro-N-(5-ciclopropil-1H-pirazol-3-il)-pirimidin-4-amina



Una mezcla de 5-ciclopropil-1H-pirazol-3-amina (246 miligramos, 2.00 milimoles), 2,4,5-tricloro-pirimidina (367 miligramos, 2.00 milimoles, 1 equivalente), y Na_2CO_3 (233 miligramos, 2.20 milimoles, 1.1 equivalentes) en EtOH (10 mililitros) se calentó a 40°C durante 16 horas. La mezcla de reacción cruda se diluyó con EtOAc, y se lavó en secuencia con: agua (3 veces), y NaCl acuoso saturado (1 vez). La capa de EtOAc resultante se secó sobre Na_2SO_4 y entonces se concentró al vacío, proporcionando la 2,5-dicloro-N-(5-ciclopropil-1H-pirazol-3-il)-pirimidin-4-amina; ESMS *m/z* 270.0 ($M+H^+$).

Intermediario 6

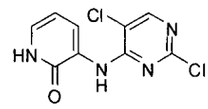
3-(2,5-dicloro-pirimidin-4-il-amino)-azepan-2-ona



Una mezcla de (±)-α-amino-ε-caprolactama (256 miligramos, 2.0 milimoles), 2,4,5-tricloro-pirimidina (366 miligramos, 2.0 milimoles, 1 equivalente), y $NaHCO_3$ (168 miligramos, 2 milimoles, 1 equivalente) en una mezcla de metanol (12 mililitros), y H_2O (6 mililitros) se agitó a temperatura ambiente durante 15 horas. El precipitado resultante se recolectó mediante filtración al vacío, y se lavó con pequeñas cantidades de metanol y agua, proporcionando el producto de 3-(2,5-dicloro-pirimidin-4-il-amino)-azepan-2-ona; ESMS *m/z* 275.0 ($M + H^+$).

Intermediario 7

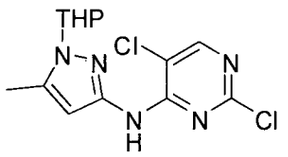
3-(2,5-dicloro-pirimidin-4-il-amino)-piridin-2(1H)-ona



Una mezcla de 3-amino-piridin-2(1H)-ona (99 miligramos, 0.90 milimoles), 2,4,5-tricloro-pirimidina (165 miligramos, 0.90 milimoles, 1 equivalente), y $NaHCO_3$ (76 miligramos, 0.90 milimoles, 1 equivalente) en una mezcla de metanol (6 mililitros), y H_2O (3 mililitros) se agitó a temperatura ambiente durante 24 horas. El precipitado resultante se recolectó mediante filtración al vacío, y se lavó con pequeñas cantidades de metanol y agua, proporcionando el producto de 3-(2,5-dicloro-pirimidin-4-il-amino)-piridin-2(1H)-ona; ESMS *m/z* 257.0 ($M + H^+$).

Intermediario 8

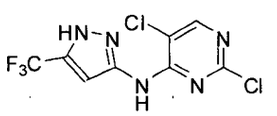
2,5-dicloro-N-(5-metil-1-(tetrahidro-2H-piran-2-il)-1H-pirazol-3-il)-pirimidin-4-amina



A una mezcla de 2,5-dicloro-N-(5-metil-1H-pirazol-3-il)-pirimidin-4-amina (2.44 gramos, 10 milimoles), y monohidrato del ácido 4-toluen-sulfónico (1.9 gramos, 10 milimoles) en tetrahidrofurano (200 mililitros), se le agregó DHP (4.25 gramos, 50 milimoles). Después de agitar durante la noche, la reacción se hizo transparente. Después de la concentración, el residuo se disolvió en acetato de etilo y se lavó con una solución acuosa saturada de Na_2CO_3. La capa orgánica se lavó entonces con salmuera, se secó sobre sulfato de sodio, y se concentró al vacío, para proporcionar la 2,5-dicloro-N-(5-metil-1-(tetrahidro-2H-piran-2-il)-1H-pirazol-3-il)-pirimidin-4-amina como un sólido amarillo claro, la cual se utilizó en las siguientes reacciones sin mayor purificación; ESMS *m/z* 244 (M-THP+H^+); TLC Rf=0.6 (Sílice; 1:1 de acetato de etilo/hexanos; material de partida Rf=0.2).

Intermediario 9

2,5-dicloro-*N*-(5-(trifluoro-metil)-1*H*-pirazol-3-il)-pirimidin-4-amina



Paso 1: 5-(trifluoro-metil)-1*H*-pirazol-3-amina

Una mezcla de (*E*)-4-amino-4-etoxi-1,1,1-trifluoro-but-3-en-2-ona (5.00 gramos, 27 milimoles), e hidrazina (1.05 gramos) en EtOH anhidro (20 mililitros) se agitó a 80°C en un frasco sellado durante la

noche. La reacción se apagó con agua (50 mililitros), y se extrajo con EtOAc (100 mililitros, y luego 50 mililitros, 2 veces). Las capas de EtOAc se combinaron y se lavaron en secuencia con agua (25 mililitros), salmuera (25 mililitros), se secaron sobre Na_2SO_4 y se evaporaron, para dar un residuo oleoso color café claro. El producto crudo se purificó mediante cromatografía en sílice (gradiente del 30 al 100 por ciento de EtOAc en hexanos), para dar la 5-(trifluoro-metil)-1*H*-pirazol-3-amina como un sólido grisáceo; ESMS m/z 152.0 ($M+H^+$).

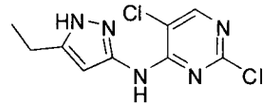
Paso 2: 2,5-dicloro-*N*-(5-(trifluoro-metil)-1*H*-pirazol-3-il)-pirimidin-4-amina

Una mezcla de 5-(trifluoro-metil)-1*H*-pirazol-3-amina (500 miligramos, 3.3 milimoles), 2,4,5-tricloro-pirimidina (607 miligramos, 3.3 milimoles), y carbonato de sodio (525 miligramos, 5 milimoles) en EtOH anhidro (10 mililitros) se agitó a temperatura ambiente. Después de un día, la LCMS mostró que la reacción no estaba completa. Se agregaron 2,4,5-tricloro-pirimidina (0.15 mililitros), y carbonato de sodio (525 miligramos) adicionales, y la reacción se continuó durante dos días más. El solvente se evaporó, y el residuo se extrajo con dicloro-metano (20 mililitros, 3 veces). Las capas de dicloro-metano combinadas se lavaron con salmuera (10 mililitros), se secaron sobre Na_2SO_4 y se evaporaron. El producto crudo se purificó mediante cromatografía en sílice (gradiente del 0 al 50 por ciento de EtOAc en hexanos), para dar la 2,5-dicloro-*N*-(5-(trifluoro-metil)-1*H*-pirazol-3-il)-pirimidin-4-amina como un sólido color

bronceado claro; ESMS m/z 297.9 ($M+H^+$).

Intermediario 10

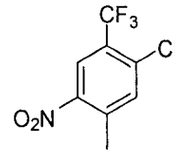
2,5-dicloro-*N*-(5-etil-1*H*-pirazol-3-il)-pirimidin-4-amina



Una mezcla de 5-etil-1*H*-pirazol-3-amina (1.00 gramos, 6.77 milimoles), 2,4,5-tricloro-pirimidina (1.24 gramos, 6.77 milimoles), y Na_2CO_3 (1.79 gramos, 16.9 milimoles) en isopropanol (15 mililitros) se agitó en un frasco sellado a temperatura ambiente durante dos días. Se agregó agua (10 mililitros). El sólido se recolectó mediante filtración, se lavó con agua (10 mililitros), y se secó para dar la 2,5-dicloro-N-(5-etil-1H-pirazol-3-il)-pirimidin-4-amina como un sólido amarillo claro; ESMS m/z 258.0 ($M+H^+$).

Intermediario 11

1-cloro-5-metil-4-nitro-2-(trifluoro-metil)-benceno



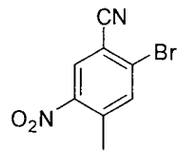
A una solución de 2-cloro-4-metil-1-(trifluoro-metil)-benceno (6.65 gramos, 34.1 milimoles) en ácido sulfúrico concentrado (25 mililitros) a 0°C, se le agregó nitrato de potasio (3.46 gramos, 34.1 milimoles) en ácido sulfúrico (15 mililitros). Después de agitar a 0°C durante 1.5 horas, la mezcla de reacción se vertió en 500 mililitros de agua helada. El precipitado se recolectó mediante filtración y se lavó con cantidades copiosas de agua, proporcionando el 1-cloro-5-

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fluoro-4-nitro-2-(trifluoro-metil)-benceno como un sólido color naranja; ^{1}H RMN (400 MHz, cloroformo-d) δ 8.356 (s, 1H), 7.543 (s, 1H), 2.660 (s, 3H).

Intermediario 12

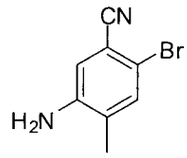
2-bromo-4-metil-5-nitro-benzonitrilo



Siguiendo el mismo procedimiento como se describe para el Intermediario 11, empezando con 2-bromo-4-metil-benzonitrilo, se obtuvo el 2-bromo-4-metil-5-nitro-benzonitrilo como un sólido amarillo; ^{1}H RMN (400 MHz, cloroformo-d) δ 8.290 (s, 1H), 7.742 (s, 1H), 2.683 (s, 3H).

Intermediario 13

5-amino-2-bromo-4-metil-benzonitrilo

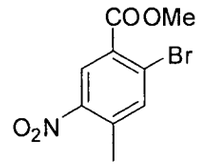


A una solución de 2-bromo-4-metil-5-nitro-benzonitrilo (500 miligramos, 2.07 milimoles) en etanol (20 mililitros), se le agregó cloruro de estaño (785 miligramos, 4.14 milimoles). La mezcla se puso a reflujo durante 5 horas. Después de enfriar a temperatura ambiente, se agregó trietil-amina (1.01 gramos, 10 milimoles). La mezcla se concentró y se purificó mediante cromatografía en sílice (gradiente del 30 al 50 por ciento de acetato de etilo en hexanos),

para proporcionar el 5-amino-2-bromo-4-metil-benzonitrilo como un sólido color beige; ESMS *m/z* 211 ($M + H^+$).

Intermediario 14

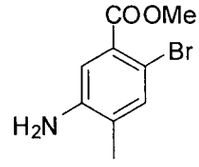
2-bromo-4-metil-5-nitro-benzoato de metilo



Siguiendo el mismo procedimiento como se describe para el Intermediario 11, empezando con 2-bromo-4-metil-benzoato de metilo, se obtuvo el compuesto del título como un sólido blanco; ^1H RMN (400 MHz, cloroformo-d) δ 8.505 (s, 1H), 7.711 (s, 1H), 3.967 (s, 3H), 2.640 (s, 3H).

Intermediario 15

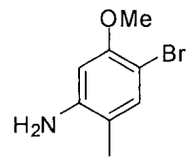
5-amino-2-bromo-4-metil-benzoato de metilo



Siguiendo el mismo procedimiento como se describe para el Intermediario 13, se obtuvo el compuesto del título como un sólido color beige; ESMS *m/z* 244 ($M + H^+$).

Intermediario 16

4-bromo-5-metoxi-2-metil-anilina



Paso 1: N-(5-metoxi-2-metil-fenil)-acetamida

A una solución de trietil-amina (2.9 gramos, 14.4 milimoles), y 5-metoxi-2-metil-anilina (1.0 gramos, 7.2 milimoles) en dicloro-metano (30 mililitros) a 0°C, se le agregó por goteo cloruro de acetilo (0.57 gramos, 7.2 milimoles). La mezcla se agitó a temperatura ambiente durante 1 hora. La reacción se apagó con una solución acuosa saturada de cloruro de amonio, y se extrajo con dicloro-metano. La capa orgánica se secó sobre Na_2SO_4 y se concentró, para dar la N-(5-metoxi-2-metil-fenil)-acetamida como cristales en forma de agujas. El producto crudo se utilizó en el siguiente paso sin mayor purificación.

Paso 2: N-(4-bromo-5-metoxi-2-metil-fenil)-acetamida

A una solución de N-(5-metoxi-2-metil-fenil)-acetamida en ácido acético (40 mililitros), se le agregó Br_2 (3 gramos, 19 milimoles) lentamente. La mezcla se tapó y se agitó a 50°C durante 5 horas. La reacción se enfrió a temperatura ambiente, entonces se apagó con una solución acuosa de sulfito de sodio, y se extrajo con acetato de etilo (50 mililitros, 3 veces). La capa orgánica combinada se secó sobre Na_2SO_4 y se concentró, para dar la N-(4-bromo-5-metoxi-2-metil-fenil)-acetamida cruda como un aceite color café, el cual se utilizó en el siguiente paso sin mayor purificación.

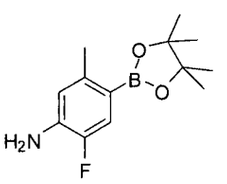
Paso 3: 4-bromo-5-metoxi-2-metil-anilina

La N-(4-bromo-5-metoxi-2-metil-fenil)-acetamida se disolvió en metanol (15 mililitros), y HCl concentrado (30 mililitros). La mezcla se puso a reflujo a 95°C durante la noche. Después de enfriar a

temperatura ambiente, la mezcla se vertió en agua helada, y se basificó a un pH = 12 con una solución acuosa concentrada de NaOH. La mezcla se extrajo entonces con acetato de etilo (50 mililitros, 3 veces). La capa orgánica combinada se secó sobre Na_2SO_4 y se concentró. El producto crudo se purificó mediante cromatografía en sílice (acetato de etilo al 15 por ciento en hexanos), para dar la 4-bromo-5-metoxi-2-metil-anilina como un sólido color beige; ^1H RMN (400 mHz, $CDCl_3$) 7.20 (s, 1H), 6.37 (s, 1H), 4.6 (br, 2H), 3.82 (s, 3H), 2.12 (s, 3H).

Intermediario 17

2-fluoro-5-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-anilina



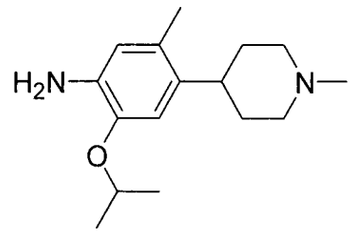
Una mezcla de 4-bromo-2-fluoro-5-metil-anilina (2.0 gramos, 9.8 milimoles), bis-(pinacolato)-diboro (2.74 gramos, 10.8 milimoles), triciclohexil-fosfina (274.8 miligramos, 0.98 milimoles), $Pd_2(dba)_3$ (448.9 miligramos, 0.49 milimoles), y acetato de potasio (1.92 gramos, 19.6 milimoles) en 60 mililitros de 1,4-dioxano se desgasificó y se purgó con nitrógeno. La mezcla de reacción se calentó a 80°C durante la noche, y entonces se enfrió a temperatura ambiente. La mezcla se dividió entre EtOAc y agua, y los extractos orgánicos recolectados se secaron (Na_2SO_4), se concentraron al vacío, y se purificaron mediante cromatografía en sílice (EtOAc / Hexanos: 20 / 80), para proporcionar la 2-fluoro-5-metil-4-(4,4,5,5-

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tetrametil-1,3,2-dioxaborolan-2-il)-anilina; ESMS *m/z* 252.2 ($M + H^+$).

Intermediario 18

2-isopropoxi-5-metil-4-(1-metil-piperidin-4-il)-fenil-amina



Paso 1: 1-bromo-5-fluoro-2-metil-4-nitro-benceno

A una solución de 2-bromo-4-fluoro-1-metil-benceno (5 gramos, 26.4 milimoles) disuelto en ácido sulfúrico concentrado (20 mililitros), se le agregó nitrato de potasio (2.67 gramos, 26.4 milimoles) en ácido sulfúrico (5 mililitros) a 0°C. Después de agitar a 0°C durante 1 hora, la reacción se diluyó con agua, se extrajo con acetato de etilo (40 mililitros, 3 veces). Las fases orgánicas combinadas se lavaron con una solución saturada de bicarbonato de sodio y salmuera en secuencia, y entonces se secaron sobre Na_2SO_4. El producto crudo obtenido después de la concentración se purificó mediante cromatografía en columna de gel de sílice con solvente mixto de hexanos/EtOAc (95/5), para proporcionar el 1-bromo-5-fluoro-2-metil-4-nitro-benceno como un sólido color naranja. ^1H RMN (400 MHz, cloroformo-d) δ 7.93 (d, 1H, J = 7.6 Hz), 7.50 (d, 1H, J = 10 Hz), 2.43 (s, 3H).

Paso 2: 1-bromo-5-isopropoxi-2-metil-4-nitro-benceno

A una solución de 1-bromo-5-fluoro-2-metil-4-nitro-benceno (paso 1, 1.5 gramos, 6.4 milimoles) en 2-propanol (30 mililitros), se

le agregó carbonato de cesio (5.3 gramos, 16 milimoles). La mezcla se calentó a 50°C durante la noche. La mezcla se concentró y se dividió entre acetato de etilo y agua. La capa orgánica se concentró y el residuo se purificó mediante cromatografía en columna de gel de sílice con acetato de etilo al 5 por ciento en hexanos, para proporcionar el 1-bromo-5-isopropoxi-2-metil-4-nitro-benceno como un sólido amarillo.

Paso 3: 4-(5-isopropoxi-2-metil-4-nitro-fenil)-piridina

A una mezcla de 1-bromo-5-isopropoxi-2-metil-4-nitro-benceno (paso 2, 1 gramo, 3.65 milimoles), ácido piridin-4-borónico (490 miligramos, 4 milimoles), 2-diciclohexil-fosfino-2',6'-dimetoxi-bifenilo (300 miligramos, 0.73 milimoles), y fosfato de potasio (1.55 gramos, 7.3 milimoles) en un solvente mixto de dioxano (15 mililitros), y agua (7.5 mililitros), se le agregó tris-(dibenciliden-acetona)-dipaladio(0) (334 miligramos, 0.36 milimoles). Esta mezcla se selló y se purgó con nitrógeno durante 3 minutos, y entonces se calentó a 120°C durante 5 horas. La mezcla se enfrió a temperatura ambiente, se filtró, y el filtrado se concentró. Después de la concentración, el producto crudo se purificó mediante cromatografía por evaporación instantánea en columna de gel de sílice (acetato de etilo al 60 por ciento en hexanos), para proporcionar la 4-(5-isopropoxi-2-metil-4-nitro-fenil)-piridina a como un sólido amarillo: ESMS *m/z* 273.2 ($M + H^+$).

Paso 4: Yoduro de 4-(5-isopropoxi-2-metil-4-nitro-fenil)-1-metil-piridinio

La 4-(5-isopropoxi-2-metil-4-nitro-fenil)-piridina (paso 3, 217 miligramos, 0.797 milimoles) se disolvió en tetrahidrofurano anhidro (9 mililitros). Se agregó yodo-metano (0.10 mililitros, 1.61 milimoles, 2 equivalentes), y la reacción se agitó a 40°C en un tubo sellado durante 2 días. Los volátiles se removieron al vacío, generando el yoduro de 4-(5-isopropoxi-2-metil-4-nitro-fenil)-1-metil-piridinio como un sólido color café: ESMS m/z 287.1 (M+).

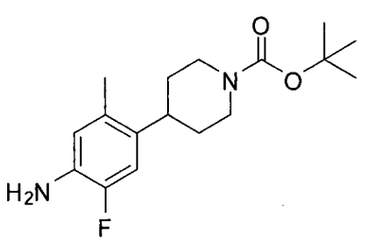
Pasos 5 y 6: 2-isopropoxi-5-metil-4-(1-metil-piperidin-4-il)-fenil-amina

El yoduro de 4-(5-isopropoxi-2-metil-4-nitro-fenil)-1-metil-piridinio (paso 4, 0.697 milimoles) se disolvió en CH_3OH (20 mililitros), y se enfrió a 0°C. Se agregó lentamente $NaBH_4$ (264 miligramos, 6.97 milimoles, 10 equivalentes). Después de que se completó esta adición, se removió el baño de enfriamiento, y la reacción se agitó a temperatura ambiente durante 1 hora. La reacción se apagó mediante la adición lenta de HCl acuoso 1N (14 mililitros). El CH_3OH se removió parcialmente al vacío. El residuo resultante se dividió entre EtOAc y NaOH acuoso 1N. Se agregó NaOH acuoso al 50 por ciento adicional hasta que la capa acuosa tuvo un pH >12. La capa de EtOAc se lavó con NaOH 1 N acuoso (2 veces), la capa orgánica entonces se secó sobre sulfato de sodio, se filtró, y se concentró al vacío. Después de la concentración, el producto crudo (175 miligramos) se disolvió en ácido acético (10 mililitros). Se agregaron ácido trifluoro-acético (0.15 mililitros, 3 equivalentes), y PtO_2 (53 miligramos, 30 por ciento en peso/peso), y

la reacción se colocó bajo gas de H_2 a 50 psi (3.5 kg/cm^2) en un agitador Parr durante 14 horas. La mezcla de reacción se filtró, y el filtrado se concentró al vacío. El residuo resultante se dividió entre EtOAc y NaOH acuoso 1N. Se agregó NaOH acuoso al 50 por ciento adicional hasta que la capa acuosa tuvo un pH >12. La capa de EtOAc se lavó con NaOH 1 N acuoso (2 veces), la capa orgánica entonces se secó sobre sulfato de sodio, se filtró, y se concentró al vacío, para dar la 2-isopropoxi-5-metil-4-(1-metil-piperidin-4-il)-fenil-amina, la cual se utilizó en los siguientes pasos sin mayor purificación: ESMS m/z 263.2 (M + H+).

Intermediario 19

4-(4-amino-5-fluoro-2-metil-fenil)-piperidin-1-carboxilato de terbutilo



Paso 1: Terbutil-éster del ácido 4-trifluoro-metan-sulfoniloxi-3,6-dihidro-2H-piridin-1-carboxílico

Una solución de *N*-terbutoxi-carbonil-4-piperidona (10.17 gramos, 0.05 moles) en tetrahidrofurano (100 mililitros), se agregó por goteo a una solución enfriada (-78°C) y vigorosamente agitada de LDA (40 mililitros de una solución 1.5M en ciclohexanos, 0.06 moles) en tetrahidrofurano (100 mililitros), bajo N_2. La mezcla de

reacción se dejó a -78°C durante 30 minutos antes de agregar una solución de fenil-trifluoro-sulfonimida (19.85 gramos, 0.055 moles) en tetrahidrofurano (50 mililitros). Entonces la mezcla de reacción se calentó a temperatura ambiente, y se agitó durante 3 horas. La reacción se apagó a 0°C con 100 mililitros de NH_4Cl acuoso saturado, y se filtró a través de Celite. El filtrado se agregó a 100 mililitros de EtOAc, y las capas se separaron. La capa orgánica se lavó con H_2O, se secó sobre $MgSO_4$ y se concentró. El producto crudo se purificó mediante cromatografía en gel de sílice (del 0 al 30 por ciento de EtOAc en hexanos como eluyente, y se verificó mediante TLC teñida con $KMnO_4$ al 2 por ciento en EtOH), para proporcionar el terbutil-éster del ácido 4-trifluoro-metan-sulfoniloxi-3,6-dihidro-2H-piridin-1-carboxílico como un aceite color amarillo.

Paso 2: 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-5,6-dihidro-piridin-1(2H)-carboxilato de terbutilo

Una solución de 4-(trifluoro-metil-sulfoniloxi)-5,6-dihidro-piridin-1(2H)-carboxilato de terbutilo (16.0 gramos, 48.2 milimoles) en sulfóxido de dimetilo (200 mililitros) se trató con bis-(pinacolato)-diboro (12.6 gramos, 49.6 milimoles), acetato de potasio (14.65 gramos, 149 milimoles), y $Pd(dppf)Cl_2$ (790 miligramos, 0.96 milimoles). La solución se purgó con N_2 (g) durante 5 minutos, y entonces se selló y se calentó a 80°C durante 15 horas. La reacción se enfrió a temperatura ambiente, y se vertió en agua helada. La mezcla se extrajo con acetato de etilo (100 mililitros, 3 veces). La fase orgánica combinada se lavó con salmuera, se secó sobre sulfato

de sodio, y se concentró al vacío. El producto crudo se purificó mediante cromatografía en gel de sílice (acetato de etilo al 15 por ciento en hexanos), para proporcionar el 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-5,6-dihidro-piridin-1(2H)-carboxilato de terbutilo como un sólido blanco.

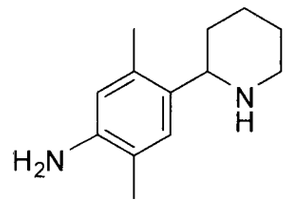
Pasos 3 y 4: 4-(4-amino-5-fluoro-2-metil-fenil)-piperidin-1-carboxilato de terbutilo

A una mezcla de 5'-cloro-N,2'-dimetil-4'-nitrobifenil-4-carboxamida (204 miligramos, 1 milimol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-5,6-dihidro-piridin-1(2H)-carboxilato de terbutilo (370 miligramos, 1.2 milimoles), y carbonato de sodio (742 miligramos, 7 milimoles) en N,N-dimetil-formamida/H_2O (12/3 mililitros), se le agregó tetraquis-(trifenil-fosfina)-paladio(0) (58 miligramos, 5 por ciento milimolar). El tubo de reacción se selló, la mezcla se purgó con N_2 durante 3 minutos, y entonces se calentó a 90°C bajo N_2 durante la noche. La reacción se enfrió a temperatura ambiente, y se vertió en una solución acuosa saturada de cloruro de amonio. La mezcla de reacción cruda se extrajo con acetato de etilo (15 mililitros, 3 veces). Los extractos orgánicos se combinaron, se lavaron con salmuera, y se concentraron. El producto crudo se purificó mediante cromatografía en gel de sílice (acetato de etilo al 20 por ciento en hexanos), para proporcionar el 4-(4-amino-5-fluoro-2-metil-fenil)-5,6-dihidro-piridin-1(2H)-carboxilato de terbutilo como un aceite color amarillo. El aceite obtenido se disolvió en metanol (20 mililitros). A la solución se le agregó Pd/C (al 10 por ciento). La

mezcla de reacción se desgasificó y se purgó con H_2 varias veces, y se agitó bajo H_2 (1 atmósfera) durante la noche. La mezcla se filtró y se concentró, para proporcionar el 4-(4-amino-5-fluoro-2-metil-fenil)-piperidin-1-carboxilato de terbutilo como un sólido blanco. ESMS *m/z* 207 (M -Boc+ H^+).

Intermediario 20

2,5-dimetil-4-(piperidin-2-il)-anilina

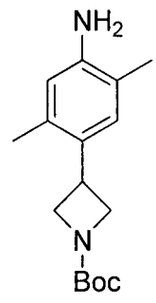


A una mezcla de 1-bromo-2,5-dimetil-4-nitro-benceno (185 miligramos, 1 milimol), y 2-(tributil-estanil)-piridina (202 miligramos, 1.1 milimoles) en N,N-dimetil-formamida (4 mililitros), se le agregó tetraquis-(trifenil-fosfina)-paladio(0) (58 miligramos, 5 por ciento milimolar). El tubo de reacción se selló, la mezcla se purgó con N_2 durante 3 minutos, y entonces se calentó a 120°C bajo N_2 durante la noche. La reacción se enfrió a temperatura ambiente, y se vertió en una solución acuosa saturada de cloruro de amonio. La mezcla de reacción cruda se extrajo con acetato de etilo (15 mililitros, 3 veces). Los extractos orgánicos se combinaron, se lavaron con salmuera, y se concentraron. El producto crudo se purificó mediante cromatografía en columna de gel de sílice (acetato de etilo al 60 por ciento en hexanos), para proporcionar la 2-(2,5-dimetil-4-nitro-fenil)-piridina como un sólido blanco. El sólido obtenido se disolvió en

ácido acético/ácido trifluoro-acético (15 mililitros/200 microlitros). A esta solución se le agregó PtO_2 (al 10 por ciento en peso/peso). La mezcla de reacción se desgasificó y se purgó con H_2 varias veces, y se agitó bajo 1 atmósfera de gas de hidrógeno durante la noche. La mezcla se filtró y se concentró, para proporcionar la 2,5-dimetil-4-(piperidin-2-il)-anilina como un aceite color amarillo. ESMS m/z 205 ($M + H^+$).

Intermediario 21

3-(4-amino-2,5-dimetil-fenil)azetidin-1-carboxilato de terbutilo



Paso 1: 3-(2,5-dimetil-4-nitro-fenil)azetidin-1-carboxilato de terbutilo

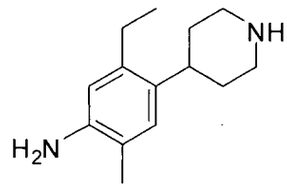
Se preparó a partir de 3-yodo-azetidin-1-carboxilato de terbutilo y 1-bromo-2,5-dimetil-4-nitro-benceno, siguiendo el protocolo general como se describe en Billotte, S. *Synlett* 1998, 379.

Paso 2: 3-(4-amino-2,5-dimetil-fenil)azetidin-1-carboxilato de terbutilo

El 3-(2,5-dimetil-4-nitro-fenil)-azetidin-1-carboxilato de terbutilo se redujo hasta el 3-(4-amino-2,5-dimetil-fenil)-azetidin-1-carboxilato de terbutilo mediante hidrogenación convencional con Níquel de Raney a temperatura ambiente utilizando metanol como el solvente.

Intermediario 22

5-etil-2-metil-4-(piperidin-4-il)-anilina



Paso 1: 4-(4-amino-5-metil-2-vinil-fenil)-5,6-dihidro-piridin-1(2H)-carboxilato de terbutilo

A una mezcla de 4-bromo-5-cloro-2-metil-anilina (500 miligramos, 2.27 milimoles), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-5,6-dihidro-piridin-1(2H)-carboxilato de terbutilo (840 miligramos, 3.73 milimoles), y carbonato de sodio (2.52 gramos, 15.9 milimoles) en N,N-dimetil-formamida/H_2O (20/5 mililitros), se le agregó tetraquis-(trifenil-fosfina)-paladio(0) (131 miligramos, 5 por ciento molar). El tubo de reacción se selló, la mezcla se purgó con N_2 durante 3 minutos, y entonces se calentó a 100°C bajo N_2 durante la noche. La reacción se enfrió a temperatura ambiente, y se vertió en una solución acuosa saturada de cloruro de amonio. La mezcla de reacción cruda se extrajo con acetato de etilo (15 mililitros, 3 veces). Los extractos orgánicos se combinaron, se lavaron con salmuera, y se concentraron. El producto crudo se purificó mediante cromatografía en gel de sílice (acetato de etilo al 80 por ciento en hexanos), para proporcionar el 4-(4-amino-2-cloro-5-metil-fenil)-5,6-dihidro-piridin-1(2H)-carboxilato de terbutilo como un sólido amarillo. Este producto obtenido (322 miligramos, 1 milimol) se disolvió en

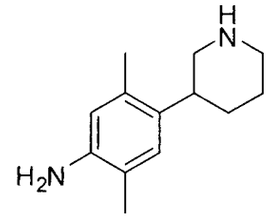
dioxano/NMP (anhidro, 4 mililitros, 3/1). A esta solución se le agregó tributil-(vinil)-estanano (380 miligramos, 1.2 milimoles), fluoruro de cesio (304 miligramos, 2 milimoles), y bis-(tri-terbutil-fosfina)-paladio (51 miligramos, 10 por ciento molar). Esta mezcla se purgó con N_2 durante 3 minutos, y entonces se calentó en un tubo sellado a 120°C durante la noche. La mezcla se enfrió a temperatura ambiente, y se diluyó con acetato de etilo. La mezcla resultante se lavó en secuencia con cloruro de amonio acuoso saturado y salmuera, y finalmente se secó sobre sulfato de sodio. Después de la concentración, el producto crudo se purificó mediante cromatografía en gel de sílice (acetato de etilo al 10 por ciento en hexanos), para proporcionar el 4-(4-amino-5-metil-2-vinil-fenil)-5,6-dihidro-piridin-1(2H)-carboxilato de terbutilo como un aceite amarillo claro; ESMS *m/z* 215.2 (M -Boc + H^+).

Paso 2: 5-etil-2-metil-4-(piperidin-4-il)-anilina

El producto obtenido a partir del paso anterior se disolvió en metanol (20 mililitros). A esta solución se le agregó HCl acuoso concentrado (200 microlitros), y óxido de platino (23 miligramos, 0.1 milimoles). La mezcla de reacción se desgasificó y se purgó con H_2 varias veces y se agitó vigorosamente bajo 1 atmósfera de H_2 durante 3 horas. La mezcla se filtró y se concentró, para proporcionar la 5-etil-2-metil-4-(piperidin-4-il)-anilina como un sólido amarillo. ESMS *m/z* 219.2 (M + H^+).

Intermediario 23

2,5-dimetil-4-(piperidin-3-il)-anilina



Paso 1: 2,5-dimetil-4-(piridin-3-il)-anilina

Una suspensión de 4-bromo-2,5-dimetil-anilina (4.00 gramos, 20 milimoles), ácido piridin-3-il-borónico (2.70 gramos, 11 milimoles), $Pd_2(dba)_3$ (0.55 gramos, 0.6 milimoles), 2-diciclohexil-fosfino-2',6'-dimetoxi-bifenilo (0.98 gramos, 1.2 milimoles), y Na_2CO_3 (10.6 gramos, 100 milimoles) en n-BuOH (50 mililitros), se desgasificó mediante una corriente de gas de argón durante 15 minutos. El matraz de la reacción se selló y se colocó en un baño de aceite previamente calentado (115°C). Después de agitar durante la noche, la reacción se enfrió, y se filtró. La torta del filtro se lavó con dicloro-metano, y el filtrado se concentró al vacío. El residuo resultante se disolvió en EtOAc (150 mililitros). El EtOAC se lavó en secuencia con agua (20 mililitros), salmuera (20 mililitros), se secó sobre Na_2SO_4 y se evaporó. El producto crudo se purificó mediante cromatografía en gel de sílice (gradiente del 0 al 50 por ciento de EtOAc en hexanos), para dar la 2,5-dimetil-4-(piridin-3-il)-anilina como un sólido amarillo; ESMS m/z 199.1 ($M+H^+$).

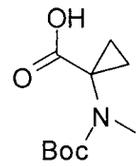
Paso 2: 2,5-dimetil-4-(piperidin-3-il)-anilina

La 2,5-dimetil-4-(piridin-3-il)-anilina (403 miligramos, 2.03 milimoles) se disolvió en metanol (5 mililitros), y HCl acuoso concentrado (1 mililitro), seguido por la adición de PtO_2 (40

miligramos). El matraz se purgó con H_2 y la reacción se agitó vigorosamente a temperatura ambiente bajo H_2 (1 atmósfera). Después de dos días, la LCMS mostró la terminación de la reacción. El catalizador se removió mediante filtración y la solución restante se concentró al vacío, para dar la 2,5-dimetil-4-(piperidin-3-il)-anilina como un sólido blanco, la cual se puede utilizar en las siguientes reacciones sin mayor purificación; ESMS m/z 205.2 ($M+H^+$).

Intermediario 24

Ácido 1-(terbutoxi-carbonil-(metil)-amino)-ciclopropan-carboxílico

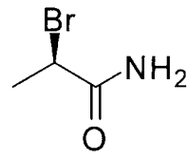


A una solución del ácido 1-(terbutoxi-carbonil-amino)-ciclopropan-carboxílico (201 miligramos, 1.0 milimoles) en N,N-dimetil-formamida (2 mililitros), se le agregó NaH (120 miligramos, 3.0 milimoles) a 0°C. La mezcla resultante se agitó a 0°C durante 10 minutos, antes de la adición de MeI (568 miligramos, 4.0 milimoles). La mezcla se calentó entonces hasta la temperatura ambiente, y se agitó durante 2 horas. A la mezcla se le agregó una solución acuosa saturada de NH_4Cl (20 mililitros), y la solución se extrajo con EtOAc (10 mililitros, 3 veces). Las capas orgánicas combinadas se concentraron, y el residuo se disolvió en metanol (3 mililitros) con NaOH (3 N, 1 mililitro). Esta mezcla se agitó a 80°C durante 1 hora, y se enfrió a temperatura ambiente. La solución transparente se purificó directamente sobre HPLC en fase inversa de preparación,

para proporcionar el ácido 1-(terbutoxi-carbonil-(metil)-amino)-ciclopropan-carboxílico. ESMS *m/z* 238.2 (M + Na^+).

Intermediario 25

(*R*)-2-bromo-propanamida



Paso 1: (*R*)-cloruro de 2-bromo-propanoílo

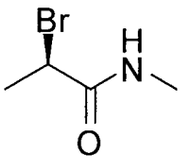
Bajo nitrógeno, a la solución del (*R*)-ácido 2-bromo-propanoico (5.0 gramos, 32.68 milimoles) en 100 mililitros de dicloro-metano, se le agregó cloruro de tionilo (7.1 mililitros, 98.04 milimoles), y 1 mililitro de dimetil-formamida en secuencia a 0°C. La reacción se agitó a temperatura ambiente durante la noche, y se concentró al vacío. El producto crudo resultante se utilizó directamente en el siguiente paso sin mayor purificación.

Paso 2: (*R*)-2-bromo-propanamida

El (*R*)-cloruro de 2-bromo-propanoílo se agregó lentamente a una solución de hidróxido de amonio al 37 por ciento en agua, enfriada a 0°C. La reacción se dejó calentar a temperatura ambiente, y se agitó durante 2 horas. El producto se extrajo con EtOAc, y los extractos orgánicos recolectados se secaron (Na_2SO_4), y se concentraron al vacío, para proporcionar la (*R*)-2-bromo-propanamida.

Intermediario 26

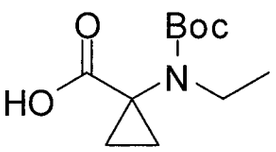
(*R*)-2-bromo-*N*-metil-propanamida



El (*R*)-cloruro de 2-bromo-propanoílo se agregó lentamente a una solución de metil-amina/agua enfriada a 0°C. La reacción se dejó calentar a temperatura ambiente, y se agitó durante 2 horas. El producto se extrajo con EtOAc, y los extractos orgánicos recolectados se secaron (Na_2SO_4), y se concentraron al vacío, para proporcionar la (*R*)-2-bromo-*N*-metil-propanamida.

Intermediario 27

Ácido 1-(terbutoxi-carbonil-(etil)-amino)-ciclopropan-carboxílico



Paso 1: 1-(terbutoxi-carbonil-(etil)-amino)-ciclopropan-carboxilato de etilo

Bajo nitrógeno, a la solución del ácido 1-(terbutoxi-carbonil-amino)-ciclopropan-carboxílico (201.2 miligramos, 1.0 milimoles) en 4 mililitros de dimetil-formamida, se le agregó NaH (120.0 miligramos, 3.0 milimoles) a 0°C. Después de 30 minutos de agitación, se agregó yodo-etano (0.4 mililitros, 5.0 milimoles), a la reacción. La reacción se calentó gradualmente a temperatura ambiente, y se agitó durante la noche. La mezcla de reacción se dividió entre EtOAc y agua. Los extractos orgánicos combinados se secaron (Na_2SO_4), y se concentraron al vacío, para proporcionar el

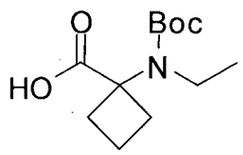
1-(terbutoxi-carbonil-(etil)-amino)-ciclopropan-carboxilato de etilo crudo, el cual se utilizó en el siguiente paso sin mayor purificación.

Paso 2: Ácido 1-(terbutoxi-carbonil-(etil)-amino)-ciclopropan-carboxílico

El producto crudo a partir del paso 1 se disolvió en una mezcla de EtOH (4.0 mililitros) y agua (1.0 mililitros). A la reacción se le agregó LiOH (82.0 miligramos, 2.0 milimoles). La reacción se calentó a 120°C en un reactor de microondas durante 10 minutos. La reacción se concentró al vacío, y el producto crudo se dividió entre EtOAc y agua. La capa de agua se neutralizó con HCl acuoso 4N a un pH de 4, y entonces se extrajo con EtOAc. Los extractos orgánicos combinados se secaron (Na_2SO_4), y se concentraron al vacío, para proporcionar el ácido 1-(terbutoxi-carbonil-(etil)-amino)-ciclopropan-carboxílico.

Intermediario 28

Ácido 1-(terbutoxi-carbonil-(etil)-amino)-ciclobutan-carboxílico



Paso 1: 1-(terbutoxi-carbonil-(etil)-amino)-ciclobutan-carboxilato de etilo

Bajo nitrógeno, a la solución del ácido 1-(terbutoxi-carbonil-amino)-ciclobutan-carboxílico (430.0 miligramos, 2.0 milimoles) en 4 mililitros de dimetil-formamida, se le agregó NaH (240.0 miligramos, 6.0 milimoles) a 0°C. Después de agitar durante 30 minutos, se

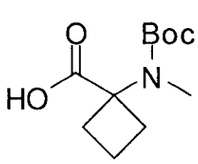
agregó yodo-etano (0.8 mililitros, 10.0 milimoles) a la reacción. La reacción se calentó a temperatura ambiente gradualmente, y se agitó durante la noche. La mezcla de reacción se dividió entre EtOAc y agua. Los extractos orgánicos combinados se secaron (Na_2SO_4), y se concentraron al vacío, para proporcionar el 1-(terbutoxi-carbonil-(etil)-amino)-ciclobutan-carboxilato de etilo crudo.

Paso 2: Ácido 1-(terbutoxi-carbonil-(etil)-amino)-ciclobutan-carboxílico

El producto crudo a partir del paso 1 se disolvió en EtOH (4.0 mililitros), y agua (1.0 mililitros). Se agregó LiOH (164.0 miligramos, 4.0 milimoles) a la reacción. La reacción se calentó a 120°C en un reactor de microondas durante 10 minutos. La reacción se concentró al vacío, y el producto crudo se dividió entre EtOAc y agua. La capa de agua se neutralizó con HCl acuoso 4N a un pH de 4, y entonces se extrajo con EtOAc. Los extractos orgánicos combinados se secaron (Na_2SO_4), y se concentraron al vacío, para proporcionar el ácido 1-(terbutoxi-carbonil-(etil)-amino)-ciclobutan-carboxílico.

Intermediario 29

Ácido 1-(terbutoxi-carbonil-(metil)-amino)-ciclobutan-carboxílico



Paso 1: M1-(terbutoxi-carbonil-(etil)-amino)-ciclobutan-carboxilato de etilo

Bajo nitrógeno, a la solución del ácido 1-(terbutoxi-carbonil-

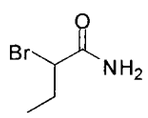
amino)-ciclobutan-carboxílico (430.0 miligramos, 2.0 milimoles) en 4 mililitros de dimetil-formamida, se le agregó NaH (240.0 miligramos, 6.0 milimoles) a 0°C. Después de agitar durante 30 minutos, se agregó yodo-metano (0.62 mililitros, 10.0 milimoles) a la reacción. La reacción se calentó a temperatura ambiente gradualmente, y se agitó durante la noche. La mezcla de reacción se dividió entre EtOAc y agua. Los extractos orgánicos combinados se secaron (Na_2SO_4), y se concentraron al vacío, para proporcionar el M1-(terbutoxi-carbonil-(etil)-amino)-ciclobutan-carboxilato de etilo crudo.

Paso 2: Ácido 1-(terbutoxi-carbonil-(metil)-amino)-ciclobutan-carboxílico

El producto crudo a partir del paso 1 se disolvió en metanol (4.0 mililitros), y agua (1.0 mililitros). Se agregó LiOH (164.0 miligramos, 4.0 milimoles) a la reacción. La reacción se calentó a 120°C en un reactor de microondas durante 10 minutos. La reacción se concentró al vacío, y el producto crudo se dividió entre EtOAc y agua. La capa de agua se neutralizó con HCl acuoso 4N a un pH de 4, y entonces se extrajo con EtOAc. Los extractos orgánicos combinados se secaron (Na_2SO_4), y se concentraron al vacío, para proporcionar el ácido 1-(terbutoxi-carbonil-(metil)-amino)-ciclobutan-carboxílico.

Intermediario 30

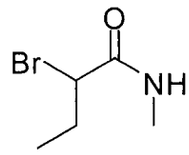
2-bromo-butanamida



Bajo nitrógeno, a una solución del ácido 2-bromo-butanoico (2.0 gramos, 12.0 milimoles) en dicloro-metano (50 mililitros) a 0°C, se le agregaron en secuencia cloruro de tionilo (2.6 mililitros, 35.9 milimoles), y 0.5 mililitros de N,N-dimetil-formamida. La reacción se dejó calentar a temperatura ambiente, y se agitó durante la noche. La mezcla de reacción se concentró al vacío, y entonces se enfrió a 0°C. Se agregaron lentamente treinta (30) mililitros de hidróxido de amonio acuoso al 37 por ciento. La reacción se dejó calentar a temperatura ambiente, y se agitó durante 2 horas, seguido por extracción con EtOAc. Los extractos orgánicos combinados se secaron (Na_2SO_4), y se concentraron al vacío, para proporcionar la 2-bromo-butanamida.

Intermediario 31

2-bromo-*N*-metil-butanamida

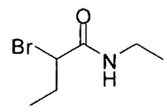


Bajo nitrógeno, a una solución del ácido 2-bromo-butanoico (2.0 gramos, 12.0 milimoles) en dicloro-metano (50 mililitros) a 0°C, se le agregaron en secuencia, cloruro de tionilo (2.6 mililitros, 35.9 milimoles), y 0.5 mililitros de N,N-dimetil-formamida. La reacción se dejó calentar a temperatura ambiente, y se agitó durante la noche. La mezcla de reacción se concentró al vacío, y entonces se enfrió a 0°C. Se agregaron lentamente treinta (30) mililitros de una solución de metil-amina/agua al 40 por ciento. La reacción se dejó calentar a

temperatura ambiente, y se agitó durante 2 horas, seguido por extracción con EtOAc. Los extractos orgánicos combinados se secaron (Na_2SO_4), y se concentraron al vacío, para proporcionar la 2-bromo-*N*-metil-butanamida.

Intermediario 32

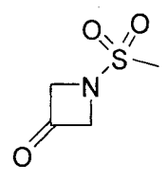
2-bromo-*N*-etil-butanamida



Bajo nitrógeno, a una solución del ácido 2-bromo-butanoico (2.0 gramos, 12.0 milimoles) en dicloro-metano (50 mililitros) a 0°C, se le agregaron en secuencia cloruro de tionilo (2.6 mililitros, 35.9 milimoles), y 0.5 mililitros de N,N-dimetil-formamida. La reacción se dejó calentar a temperatura ambiente, y se agitó durante la noche. La mezcla de reacción se concentró al vacío, y entonces se enfrió a 0°C. Se agregaron lentamente treinta (30) mililitros de una solución de etil-amina/agua al 40 por ciento. La reacción se dejó calentar a temperatura ambiente, y se agitó durante 2 horas, seguido por extracción con EtOAc. Los extractos orgánicos combinados se secaron (Na_2SO_4), y se concentraron al vacío, para proporcionar la 2-bromo-*N*-etil-butanamida.

Intermediario 33

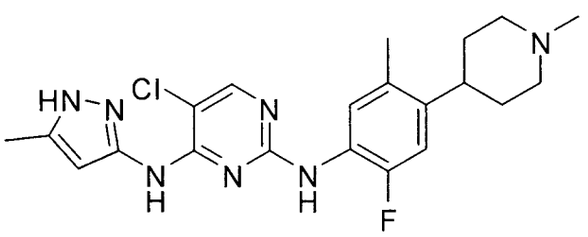
1-(metil-sulfonil)-azetidin-3-ona



A una mezcla de clorhidrato de 3-azetidinona (471 miligramos, 3.28 milimoles), y K_2CO_3 (1.50 gramos, 11 milimoles) en $CHCl_3/H_2O$ (5/5 mililitros), se le agregó anhídrido metan-sulfónico (1.14 gramos, 6.57 milimoles) en una porción a 0°C. Después de agitar durante 2 horas, la reacción se diluyó con $NaHCO_3$ acuoso saturado (5 mililitros), y se extrajo con dicloro-metano (25 mililitros, 3 veces). Las capas de dicloro-metano combinadas se lavaron con salmuera (5 mililitros), se secaron sobre Na_2SO_4 y se evaporaron, para proporcionar la 1-(metil-sulfonil)-azetidin-3-ona como un sólido grisáceo, la cual se utilizó sin mayor purificación; ^{1}H RMN (400 MHz, $CDCl_3$) δ 4.82 (s, 4H), 3.05 (s, 3H).

Ejemplo 1

5-cloro-N2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (1)



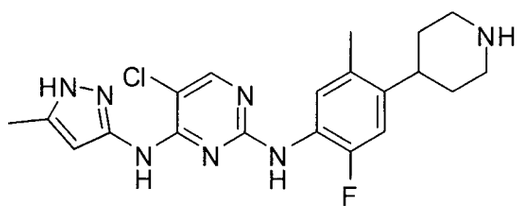
Paso 1: Una mezcla de la 2,5-dicloro-N-(5-metil-1H-pirazol-3-il)-pirimidin-4-amina (Intermediario 1, 132 miligramos, 0.54 milimoles), y 4-(4-amino-5-fluoro-2-metil-fenil)-piperidin-1-carboxilato de terbutilo (Intermediario 19, 166 miligramos, 0.54 milimoles) en 2-propanol (15 mililitros) se trató con HCl acuoso concentrado (14 gotas). La mezcla se selló y se calentó en un reactor de microondas a 130°C durante 60 minutos. La mezcla se concentró para proporcionar la 5-cloro-N2-

(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un sólido amarillo. Una porción del producto crudo se purificó mediante HPLC en fase inversa de preparación, para proporcionar la 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un sólido blanco; ESMS *m/z* 416.1 ($M + H^+$). El resto del producto crudo se utilizó directamente para el siguiente paso sin mayor purificación.

Paso 2: A una solución del producto crudo a partir del paso anterior en tetrahidrofurano (5 mililitros), y metanol (5 mililitros), se le agregaron formaldehído (100 microlitros, 1.3 milimoles), y 10 gotas de AcOH en secuencia. La mezcla de reacción se agitó a temperatura ambiente durante 1 hora, entonces se agregó cianoborohidruro de sodio (175 miligramos, 2.78 milimoles) en una porción, y la reacción se agitó durante 30 minutos adicionales. La reacción se apagó con NH_4Cl acuoso saturado y se concentró al vacío, para dar un residuo oleoso. El residuo se purificó mediante HPLC en fase inversa de preparación, para proporcionar la 5-cloro-N2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un sólido blanco. ^1H RMN (400 MHz, DMSO-d6) δ 10.33 (br, 1H), 9.90 (br, 1H0, 9.60 (br, 1H), 8.22 (s, 1H), 7.56 (d, 1H), 7.00 (d, 1H), 6.20 (s, 1H), 3.53-3.50 (m, 2H), 3.16-3.10 (m, 2H), 2.97-2.92 (m,1H), 2.81 (d, 3H), 2.26 (s, 3H), 2.16 (s, 3H), 1.94-1.91 (m, 2H), 1.83-1.73 (m, 2H); ESMS *m/z* 430.1 ($M + H^+$).

Ejemplo 2

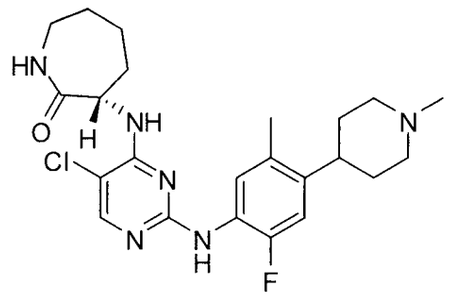
5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (2)



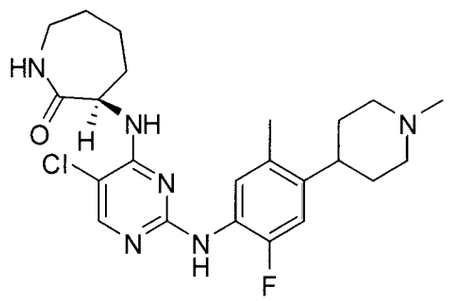
Una mezcla de 2,5-dicloro-N-(5-metil-1H-pirazol-3-il)-pirimidin-4-amina (Intermediario 1, 132 miligramos, 0.54 milimoles), y 4-(4-amino-5-fluoro-2-metil-fenil)-piperidin-1-carboxilato de terbutilo (Intermediario 19, 166 miligramos, 0.54 milimoles) en 2-propanol (15 mililitros) se trató con HCl acuoso concentrado (14 gotas). La mezcla se selló y se calentó en un reactor de microondas a 130°C durante 60 minutos. La mezcla se concentró para proporcionar la 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un sólido amarillo. Una porción del producto crudo se purificó mediante HPLC en fase inversa de preparación, para proporcionar la 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un sólido blanco; ESMS *m/z* 416.1 ($M + H^+$).

Ejemplos 3 y 4

(*S*)-3-(5-cloro-2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil-amino) pirimidin-4-il-amino)-azepan-2-ona (10)



(*R*)-3-(5-cloro-2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil-amino) pirimidin-4-il-amino)-azepan-2-ona (11)

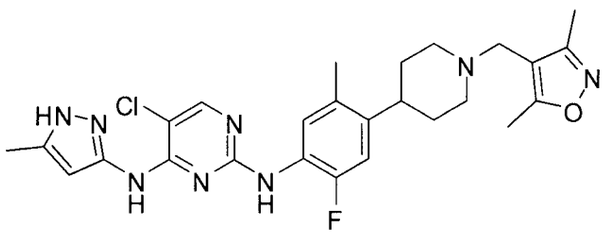


La (±)-3-(5-cloro-2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil-amino)-pirimidin-4-il-amino)-azepan-2-ona se sintetizó mediante la misma serie de procedimientos como se describe en el Ejemplo 1, utilizando el Intermediario 6 y el Intermediario 19. La separación quiral de la mezcla racémica se condujo mediante HPLC en fase normal utilizando una columna ChiralPaK AD empleando el siguiente sistema de solventes: hexanos (80 por ciento), e iPrOH (20 por ciento) modificado con dietil-amina al 0.1 por ciento. Los dos picos de los enantiómeros purificados se recolectaron por separado: (*S*)-3-(5-cloro-2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil-amino)-pirimidin-4-il-amino)-azepan-2-ona y (*R*)-3-(5-cloro-2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil-amino)-pirimidin-4-il-amino)-azepan-2-ona; ambos picos: ESMS m/z 461.2 ($M + H^+$). El pico de

elución más temprana (Rt = 7.26 minutos.), y el pico de elución más tardía (Rt = 10.17 minutos.) se asignaron arbitrariamente como los enantiómeros (*S*) y (*R*), respectivamente.

Ejemplo 5

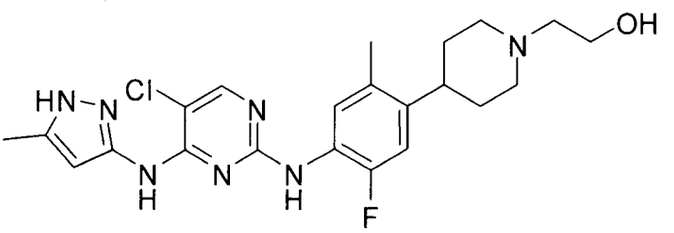
5-cloro-N2-(4-(1-((3,5-dimetil-isoxazol-4-il)-metil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (19)



A una mezcla de 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (0.12 milimoles) y trietil-amina (83 microlitros, 0.6 milimoles) en N,N-dimetil-formamida (1.5 mililitros), se le agregó 4-(cloro-metil)-3,5-dimetil-isoxazol (35 miligramos, 0.24 milimoles). La mezcla se agitó a temperatura ambiente durante 3 horas. La reacción se filtró, y el filtrado se purificó mediante HPLC en fase inversa de preparación para proporcionar la 5-cloro-N2-(4-(1-((3,5-dimetil-isoxazol-4-il)-metil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un sólido blanco. ^{1}H RMN (400 MHz, MeOD-d4) 8.12 (s, 1H), 7.75 (d, 1H), 7.03 (s, 1H), 6.27 (s, 1H), 4.25 (s, 2H), 3.69-3.67 (m, 2H), 3.27-3.20 (m, 3H), 2.54 (s, 3H), 2.37 (s, 3H), 2.34 (s, 3H), 2.30 (s, 3H), 2.10-1.95 (m, 4H);ESMS m/z 525.1 (M + H+).

Ejemplo 6

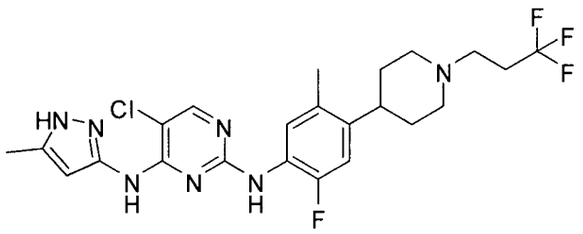
2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-etanol (22)



La 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (0.12 milimoles) se disolvió en N,N-dimetil-formamida anhidra (1 mililitro). Se agregó trietil-amina (50 microlitros, 0.36 milimoles, 3 equivalentes), seguida por 2-bromo-etanol (0.018 mililitros, 0.24 milimoles, 2 equivalentes) disuelto en N,N-dimetil-formamida anhidra (0.7 mililitros). El recipiente de reacción se selló y se calentó en un reactor de microondas a 100°C durante 20 minutos. Después de enfriar a temperatura ambiente, la reacción se concentró y el producto crudo se purificó utilizando HPLC en fase inversa de preparación para dar el 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-etanol como un sólido blanco: ESMS m/z 460.2 (M + H+).

Ejemplo 7

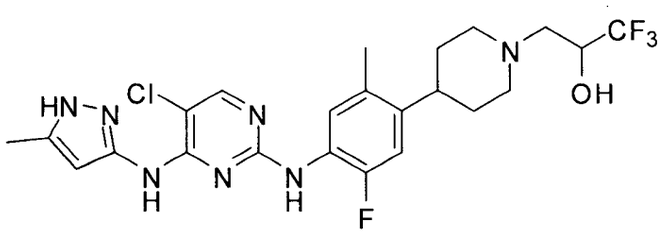
5-cloro-N^2-(2-fluoro-5-metil-4-(1-(3,3,3-trifluoro-propil)-piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (24)



La mezcla de 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (0.12 milimoles), 3-bromo-1,1,1-trifluoro-propano (85.0 microlitros, 0.60 milimoles), y trietil-amina (102.0 microlitros, 0.60 milimoles) en 2 mililitros de dimetil-formamida se agitó durante la noche. La mezcla de reacción se purificó mediante HPLC en fase inversa de preparación para proporcionar la 5-cloro-N2-(2-fluoro-5-metil-4-(1-(3,3,3-trifluoro-propil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina. ESMS m/z 512.2 ($M + H^+$).

Ejemplo 8

3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol (30)

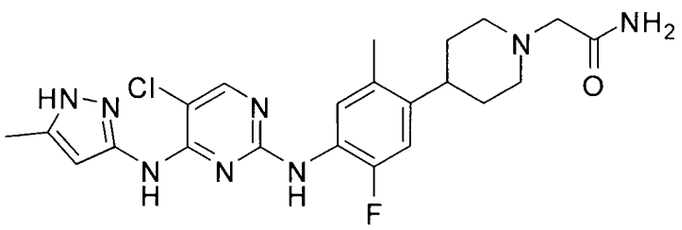


La mezcla de 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (50.0 miligramos, 0.12 milimoles), y 2-(trifluoro-metil)-oxirano (67.8 miligramos, 0.60 milimoles) en 2 mililitros de dimetil-formamida se

agitó durante la noche. La mezcla de reacción se purificó mediante HPLC en fase inversa de preparación para proporcionar el 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol. ESMS m/z 528.2 ($M + H^+$).

Ejemplo 9

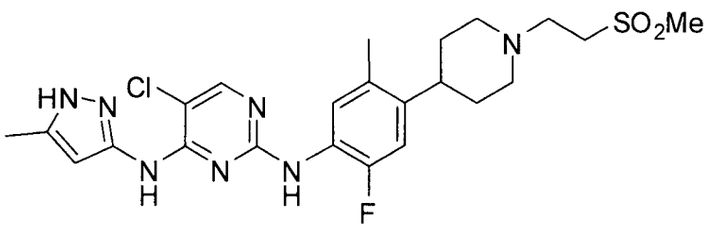
2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-acetamida (39)



A una mezcla de 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (0.12 milimoles), y trietil-amina (50 microlitros, 0.36 milimoles) en N,N-dimetil-formamida (1.5 mililitros), se le agregó 2-bromo-acetamida (33 miligramos, 0.24 milimoles). La mezcla se agitó a temperatura ambiente durante 2 horas. La reacción se filtró, y el filtrado se purificó mediante HPLC en fase inversa de preparación para dar la 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-acetamida como un sólido blanco: ^{1}H RMN (400 MHz, MeOD-d_4) δ 8.11 (s, 1H), 7.76 (d 1H), 7.09 (d, 1H), 6.27 (s, 1H), 4.0 (s, 2H), 3.75-3.73 (m, 2H), 3.22-3.13 (m, 3H), 2.34 (s, 3H), 2.30 (s, 3H), 2.04 -2.00 (m, 4H); ESMS *m/z* 473.2 ($M + H^+$).

Ejemplo 10

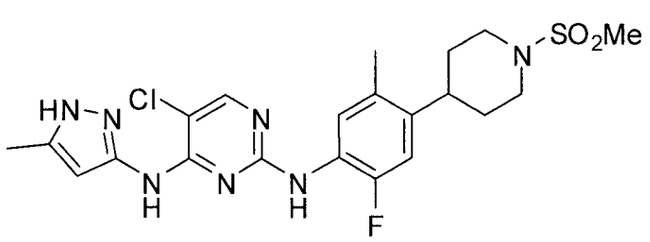
5-cloro-N2-(2-fluoro-5-metil-4-(1-(2-(metil-sulfonil)-etil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (55)



A una mezcla de 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (0.12 milimoles), y trietil-amina (83 microlitros, 0.6 milimoles) en N,N-dimetil-formamida (1.5 mililitros), se le agregó metil-vinil-sulfona (38 miligramos, 0.36 milimoles). La mezcla se agitó a temperatura ambiente durante 1 hora. La reacción se filtró, y el filtrado se purificó mediante HPLC en fase inversa de preparación, para proporcionar la 5-cloro-N2-(2-fluoro-5-metil-4-(1-(2-(metil-sulfonil)-etil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un sólido blanco. ESMS m/z 522.1 (M + H+).

Ejemplo 11

5-cloro-N2-(2-fluoro-5-metil-4-(1-(metil-sulfonil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (62)

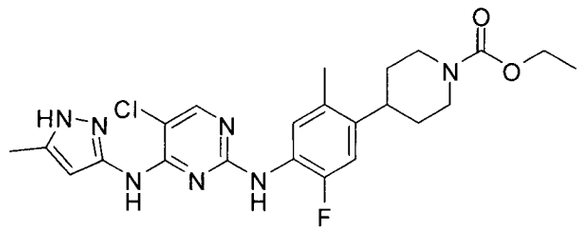


A una mezcla de 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-

fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (0.12 milimoles), y trietil-amina (50 microlitros, 0.36 milimoles) en N,N-dimetil-formamida (1.5 mililitros), se le agregó cloruro de metan-sulfonilo (18 microlitros, 0.24 milimoles). La mezcla se agitó a temperatura ambiente durante 2 horas. La reacción se filtró, y el filtrado se purificó mediante HPLC en fase inversa de preparación para dar la 5-cloro-N2-(2-fluoro-5-metil-4-(1-(metil-sulfonil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un sólido blanco: ESMS *m/z* 494.2 ($M + H^+$).

Ejemplo 12

4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-carboxilato de etilo (66)

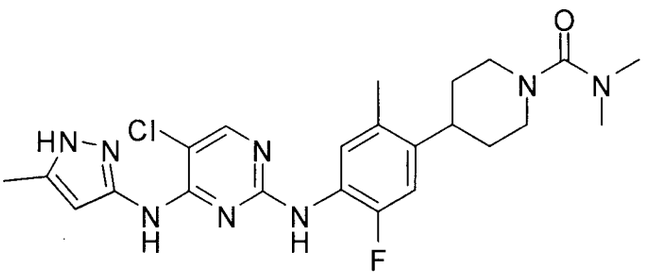


A una mezcla de 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (0.12 milimoles), y trietil-amina (50 microlitros, 0.36 milimoles) en N,N-dimetil-formamida (1.5 mililitros), se le agregó cloro-formato de etilo (26 miligramos, 0.24 milimoles). La mezcla se agitó a temperatura ambiente durante 2 horas. La reacción se filtró, y el filtrado se purificó mediante HPLC en fase inversa de preparación, para dar el 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-carboxilato de etilo como un sólido

blanco: ^{1}H RMN (400 MHz, MeOD-d_4) δ 8.13 (s, 1H), 7.54 (d, 1H), 7.10 (d, 1H), 6.28 (s, 1H), 4.30-4.26 (m, 2H), 4.14 (q, 2H), 2.99-2.96 (m, 3H), 2.33 (s, 3H), 2.29 (s, 3H), 1.8-1.77 (m, 2H), 1.64-1.55 (m, 2H), 1.28 (t, 3H); ESMS *m/z* 488.2 (M + H$^+$).

Ejemplo 13

4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-N,N-dimetil-piperidin-1-carboxamida (69)

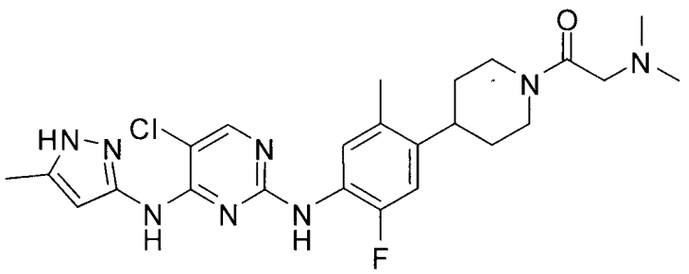


A una mezcla de 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (0.12 milimoles), y trietil-amina (83 microlitros, 0.6 milimoles) en N,N-dimetil-formamida (1.5 mililitros), se le agregó cloruro dimetil-carbámico (39 miligramos, 0.36 milimoles). La mezcla se agitó a temperatura ambiente durante 1 hora. La reacción se filtró, y el filtrado se purificó mediante HPLC en fase inversa de preparación, para proporcionar la 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-N,N-dimetil-piperidin-1-carboxamida como un sólido blanco. ESMS m/z 487.2 (M + H+).

Ejemplo 14

1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona

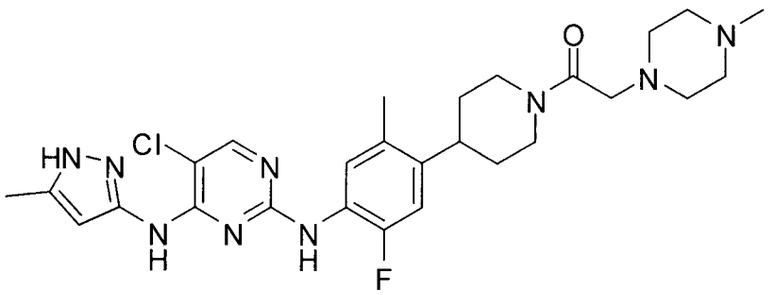
(73)



A una mezcla de 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (0.12 milimoles), y trietil-amina (50 microlitros, 0.36 milimoles) en N,N-dimetil-formamida (1.5 mililitros), se le agregó cloruro de 2-(dimetil-amino)-acetilo (38 miligramos, 0.24 milimoles). La mezcla se agitó a temperatura ambiente durante 1 hora. La reacción se filtró, y el filtrado se purificó mediante HPLC en fase inversa de preparación, para dar la 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona como un sólido blanco: ^{1}H RMN (400 MHz, MeOD-d_4) δ 8.08 (s, 1H), 7.71 (d, 1H), 7.03 (d, 1H), 6.26 (s, 1H), 4.71-4.67 (m, 2H), 3.81-3.77 (m, 2H), 3.14-3.12 (m, 2H), 2.98 (s, 3H), 2.96 (s, 3H), 2.90-2.83 (m, 1H), 2.34 (s, 3H), 2.28 (s, 3H), 1.87 (d, 2H), 1.76-1.55 (m, 2H); ESMS *m/z* 501.2 (M + H$^+$).

Ejemplo 15

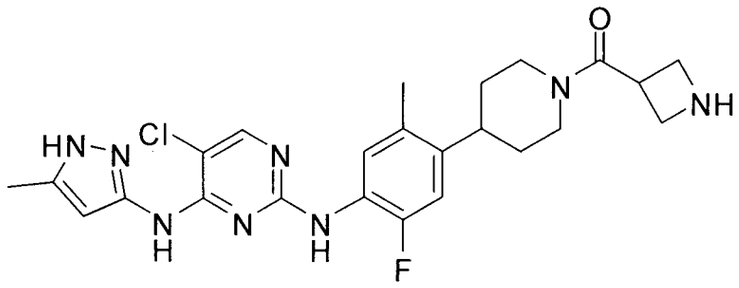
1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(4-metil-piperazin-1-il)-etanona (105)



A la solución de 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (100.0 miligramos, 0.24 milimoles) en 4 mililitros de dicloro-metano se le agregaron cloruro de 2-cloro-acetilo (23.0 microlitros, 0.29 milimoles), y trietil-amina (67.0 microlitros, 0.48 milimoles), en secuencia. La reacción se agitó a temperatura ambiente durante 1 hora, y luego se lavó con salmuera. El extracto orgánico se secó sobre Na_2SO_4, seguido por concentración al vacío, para proporcionar un producto crudo. El producto crudo se mezcló con 1-metil-piperazina (116.0 miligramos, 1.16 milimoles) en 3 mililitros de dimetil-formamida, y la reacción se agitó durante la noche a temperatura ambiente. La mezcla de reacción se purificó mediante HPLC de preparación, para proporcionar la 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(4-metil-piperazin-1-il)-etanona. ESMS m/z 556.3 ($M + H^+$).

Ejemplo 16

Azetidin-3-il-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-metanona (131)



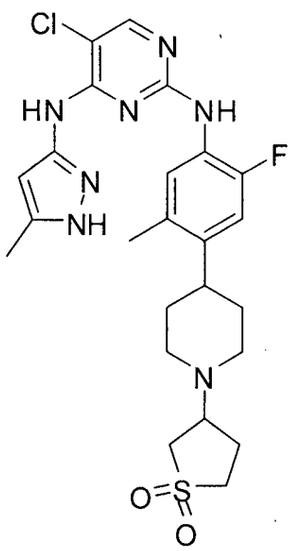
A una mezcla de 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (0.12 milimoles), di-isopropil-etil-amina (50 microlitros, 0.36 milimoles), y HATU (55 miligramos, 0.14 milimoles) en N,N-dimetil-formamida (1.5 mililitros), se le agregó ácido 1-(terbutoxi-carbonil)-azetidin-3-carboxílico (29 miligramos, 0.14 milimoles). Después de agitar a temperatura ambiente durante 4 horas, la mezcla se diluyó con metanol (1 mililitro), y HCl acuoso concentrado (1 mililitro). La mezcla se agitó a 50°C durante 30 minutos. La mezcla se filtró y se purificó mediante HPLC en fase inversa de preparación, para dar la azetidin-3-il-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-metanona como un sólido blanco. ^{1}H RMN (400 MHz, MeOD-d_4) δ 8.08 (s, 1H), 7.68 (d, 2H), 7.04 (d, 2H), 6.26 (s, 1H), 4.74-4.68 (m, 2H), 4.39-4.35 (m, 1H), 4.29-4.24 (m, 2H), 4.11 -4.07 (m, 1H), 3.74-3.71 (m, 1H), 3.25 -3.24 (m, 1H), 3.07-3.04 (m, 1H), 2.87-2.80 (m, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 1.87-1.84 (m, 2H), 1.66-1.56 (m, 2H); ESMS *m/z* 499.2 (M + H$^+$).

Ejemplo 17

5-cloro-N^2-(2-fluoro-5-metil-4-(1-(tetrahidro-1,1-dioxido-3-tienil)-

piperidin-4-il)-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina

(145)

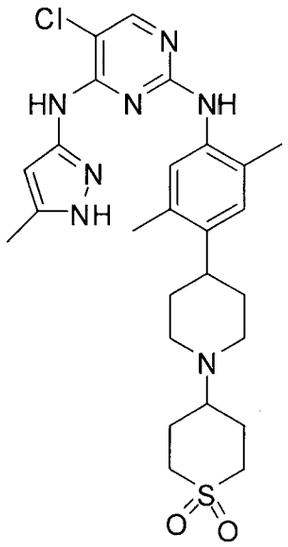


A la 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (30 miligramos, 0.072 milimoles) en EtOH (0.5 mililitros), se le agregó tiofen-2,3-dihidro-1,1-dióxido (17 miligramos, 0.144 milimoles). La mezcla resultante entonces se calentó a 130°C durante 2 horas. Después de enfriarse a temperatura ambiente, la mezcla se concentró y se purificó mediante HPLC en fase inversa de preparación, para proporcionar la 5-cloro-N2-(2-fluoro-5-metil-4-(1-(tetrahidro-1,1-dioxido-3-tienil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina. ESMS m/z 534.2 (M + H$^+$).

Ejemplo 18

5-cloro-N^2-(2,5-dimetil-4-(1-(tetrahidro-1,1-dioxido-2H-tiopiran-4-il))-piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

(146)



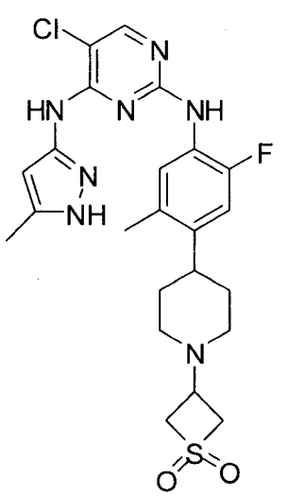
Paso 1: A una solución de 5-cloro-N2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (30 miligramos, .073 milimoles) en acetonitrilo (1 mililitro), se le agregaron Cs_2CO_3 (47 miligramos, 0.15 milimoles), y 4-yodo-tetrahidro-2H-tiopirano (48 miligramos, 0.22 milimoles). Esta mezcla entonces se agitó a 80°C durante 16 horas. Después de enfriarse a temperatura ambiente, la mezcla se trató con una solución acuosa saturada de NH_4Cl (3 mililitros), y se extrajo con EtOAc (3 mililitros, 3 veces). Las capas orgánicas se combinaron y se concentraron. El residuo se purificó mediante cromatografía en gel de sílice (Gradiente de aproximadamente el 0 al 8 por ciento de $MeOH/CH_2Cl_2$ con NH_3), para proporcionar la 5-cloro-N2-(2,5-dimetil-4-(1-(tetrahidro-2H-tiopiran-4-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un sólido blanco. ESMS m/z 512.2 ($M + H^+$).

Paso 2: A la 5-cloro-N2-(2,5-dimetil-4-(1-(tetrahidro-2H-tiopiran-4-

il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (18 miligramos, .035 milimoles) en CH_2Cl_2 (1 mililitro), se le agregó m-CPBA (16 miligramos, .0.71 milimoles) a 0°C. La mezcla se calentó entonces hasta la temperatura ambiente, y se agitó durante 30 minutos; entonces se agregó una solución acuosa saturada de $NaHCO_3$ (3 mililitros) y el producto crudo se extrajo con CH_2Cl_2 (3 mililitros, 3 veces). Las capas orgánicas combinadas se concentraron y se purificaron mediante cromatografía de capa delgada de preparación (gel de sílice, 12 por ciento de MeOH/CH_2Cl_2 con NH_3), para proporcionar la 5-cloro-N2-(2,5-dimetil-4-(1-(tetrahidro-1,1-dioxido-2H-tiopiran-4-il))-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina. ESMS m/z 544.2 ($M + H^+$).

Ejemplo 19

5-cloro-N^2-(2-fluoro-5-metil-4-(1-(1,1-dioxido-3-tietanil)-piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (148)

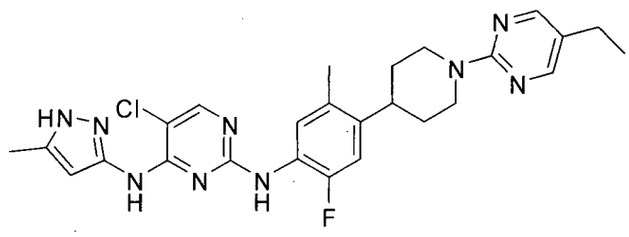


A la 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (30 miligramos, 0.072

milimoles) en metanol (1 mililitro), se le agregó 1,1-dióxido de 3-bromo-tietano (15 miligramos, 0.079 milimoles), seguido por trietil-amina (15 miligramos). La mezcla resultante se agitó a temperatura ambiente durante 5 horas, y entonces se concentró. El residuo resultante se purificó mediante HPLC en fase inversa de preparación, para proporcionar la 5-cloro-N2-(2-fluoro-5-metil-4-(1-(1,1-dioxido-3-tietanil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina. ^{1}H RMN (400 MHz, DMSO-d6 + 1 gota de D_2O) δ 8.02 (s, 1H), 7.37 (s, 1H), 7.02 (s, 1H), 6.23 (s, 1H), 4.28-4.22 (m, 2H), 4.12-4.07 (m, 2H), 3.22-3.18 (m, 1H), 2.95-2.92 (m, 2H), 2.68-2.62 (m, 1H), 2.22 (s, 3H), 2.13 (s, 3H), 2.07-2.01 (m, 2H), 1.71-1.55 (m, 4H). ESMS m/z 520.2 ($M + H^+$).

Ejemplo 20

5-cloro-N2-(4-(1-(5-etil-pirimidin-2-il)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (149)

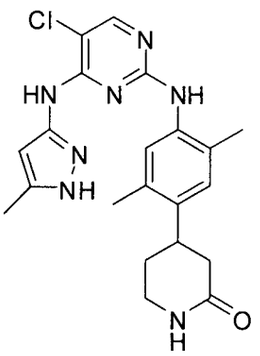


A una mezcla de 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (0.10 milimoles), y trietil-amina (83 microlitros, 0.6 milimoles) en N,N-dimetil-formamida (1.5 mililitros), se le agregó 2-cloro-5-etil-pirimidina (27 miligramos, 0.20 milimoles). La mezcla se calentó en un reactor de microondas a 120°C durante 10 minutos. La reacción se filtró, y el

filtrado se purificó mediante HPLC en fase inversa de preparación, para proporcionar la 5-cloro-N2-(4-(1-(5-etil-pirimidin-2-il)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un sólido blanco. ESMS m/z 522.2 (M + H+).

Ejemplo 21

4-(4-(5-cloro-4-(5-metil-*1H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-2-ona (151)



Paso 1: En un tubo de reacción de microondas de 5 mililitros se agregaron 2-(2,5-dimetil-4-nitro-fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (143 miligramos, 0.516 milimoles, se preparó a partir de 1-bromo-2,5-dimetil-4-nitro-benceno mediante el protocolo convencional), 1-(4-metoxi-bencil)-5,6-dihidro-piridin-2(1H)-ona (56 miligramos, 0.26 milimoles, se preparó siguiendo un procedimiento similar al reportado por Lerchner y colaboradores, en Chem. Eur. J. 2006, 12, 8208), dímero de cloro-(1,5-ciclo-octadieno)-rodio (I) (13 miligramos, .026 milimoles), KOH (0.13 mililitros, solución acuosa 1N), y dioxano (1.2 mililitros). El tubo se desgasificó, se rellenó con N_2 y se selló. El tubo de reacción entonces se calentó a 100°C en un reactor de microondas durante 10 minutos. Después de que se abrió

el tubo de reacción, la mezcla se trató con una solución acuosa saturada de NH_4Cl (3 mililitros), y se extrajo con EtOAc (4 mililitros, 3 veces). Las capas orgánicas se combinaron y se concentraron. El residuo se purificó mediante cromatografía en columna por evaporación instantánea (gel de sílice, gradiente del 0 por ciento a aproximadamente el 70 por ciento de EtOAc/hexano), para proporcionar la 4-(2,5-dimetil-4-nitro-fenil)-1-(4-metoxi-bencil)-piperidin-2-ona. ESMS m/z 369.2 ($M + H^+$).

Paso 2: A la 4-(2,5-dimetil-4-nitro-fenil)-1-(4-metoxi-bencil)-piperidin-2-ona (63 miligramos, 0.17 milimoles) en metanol (10 mililitros), se le agregó el 10 por ciento en peso/peso de Pd/C (6 miligramos), la mezcla se desgasificó y se agitó bajo H_2 a temperatura ambiente durante 14 horas. Después de remover el catalizador mediante filtración, el filtrado se concentró para proporcionar la 4-(4-amino-2,5-dimetil-fenil)-1-(4-metoxi-bencil)-piperidin-2-ona como un aceite amarillento pálido. ESMS m/z 339.2 ($M + H^+$).

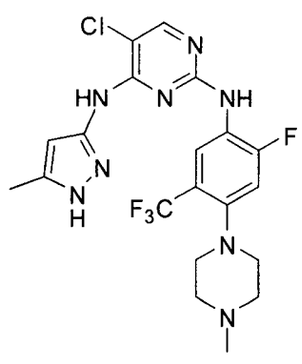
Paso 3: A una mezcla de la 4-(4-amino-2,5-dimetil-fenil)-1-(4-metoxi-bencil)-piperidin-2-ona (23 miligramos, 0.094 milimoles), y 2,5-dicloro-N-(5-metil-1H-pirazol-3-il)-pirimidin-4-amina (29 miligramos, 0.086 milimoles) en iPrOH (1 mililitro), se le agregó HCl (60 microlitros, 4N en dioxano). El recipiente de reacción entonces se selló y se calentó a 130°C durante 4 horas. Después de enfriar a temperatura ambiente, la mezcla se trató con una solución acuosa saturada de $NaHCO_3$ (3 mililitros), y se extrajo con EtOAc (4

mililitros, 3 veces). Las capas orgánicas se combinaron y se concentraron. El residuo se purificó mediante cromatografía en columna por evaporación instantánea (gel de sílice, gradiente del 0 a aproximadamente el 10 por ciento de $MeOH/CH_2Cl_2$), para proporcionar la 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-1-(4-metoxi-bencil)-piperidin-2-ona. ESMS m/z 546.2 ($M + H^+$).

Paso 4: Una solución de 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-1-(4-metoxi-bencil)-piperidin-2-ona (45 miligramos) en ácido trifluoro-acético (0.5 mililitros) se calentó a 100°C durante 24 horas. Después de enfriarse a temperatura ambiente, la mezcla se concentró y se purificó mediante HPLC en fase inversa de preparación, para proporcionar la 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-2-ona. ESMS m/z 426.2 ($M + H^+$).

Ejemplo 22

5-cloro-N^2-(2-fluoro-4-(4-metil-piperazin-1-il)-5-(trifluoro-metil)-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina (157)



Paso 1: A un tubo de reacción de microondas se le agregó la 4-

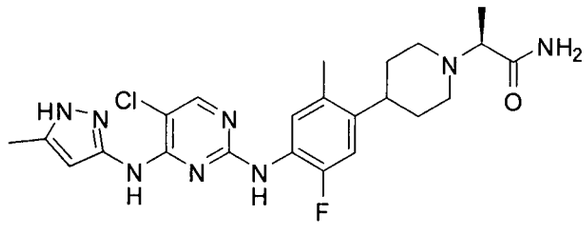
bromo-2-fluoro-5-(trifluoro-metil)-anilina (256 miligramos, 1.0 milimoles), 1-metil-piperazina (300 miligramos, 3 milimoles), $Pd_2(dba)_3$ (91.5 miligramos, 0.1 milimoles), diterbutil-(2',4',6'-tri-isopropil-bifenil-2-il)-fosfina (60 miligramos, 0.2 milimoles), NaOtBu (144 miligramos, 1.5 milimoles), y tetrahidrofurano (3 mililitros). Después de que el tubo de reacción se desgasificó y se rellenó con N_2, el tubo se calentó a 120°C en un reactor de microondas durante 40 minutos. La mezcla se vertió entonces en una solución acuosa saturada de NH_4Cl (10 mililitros), y se extrajo con EtOAc (10 mililitros, 3 veces). Las capas orgánicas se combinaron y se concentraron. El residuo se purificó mediante cromatografía en columna por evaporación instantánea (gel de sílice, gradiente de $MeOH/CH_2Cl_2$, del 0 a aproximadamente el 10 por ciento), para proporcionar la 2-fluoro-4-(4-metil-piperazin-1-il)-5-(trifluoro-metil)-anilina como un sólido blanco. ESMS m/z 278.1 ($M + H^+$).

Paso 2: A una mezcla de la 2-fluoro-4-(4-metil-piperazin-1-il)-5-(trifluoro-metil)-anilina (37 miligramos, 0.133 milimoles), y 2,5-dicloro-N-(5-metil-1H-pirazol-3-il)-pirimidin-4-amina (36 miligramos, 0.147 milimoles) en iPrOH (1 mililitro), se le agregó HCl (100 microlitros, 4N en dioxano). El recipiente de reacción entonces se selló y se calentó a 130°C durante 4 horas. Después de enfriar a temperatura ambiente, la mezcla se trató con una solución acuosa saturada de $NaHCO_3$ (5 mililitros), y se extrajo con EtOAc (5 mililitros, 3 veces). Las capas orgánicas se combinaron y se concentraron. El residuo se purificó mediante cromatografía de capa

delgada de preparación (gel de sílice, 8 por ciento de $MeOH/CH_2Cl_2$), para proporcionar la 5-cloro-N2-(2-fluoro-4-(4-metil-piperazin-1-il)-5-(trifluoro-metil)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina. ESMS m/z 485.2 ($M + H^+$).

Ejemplo 23

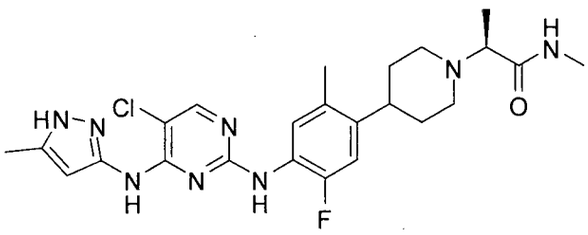
(*S*)-2-(4-(4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propanamida (163)



Una mezcla de la 5-cloro-N^2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (50.0 miligramos, 0.12 milimoles), (*R*)-2-bromo-propanamida (90.6 miligramos, 0.60 milimoles), y trietil-amina (102.0 microlitros, 0.60 milimoles) en 2 mililitros de dimetil-formamida, se calentó a 150°C en un reactor de microondas durante 30 minutos. La mezcla de reacción se purificó directamente mediante HPLC en fase inversa de preparación, para proporcionar la (*S*)-2-(4-(4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propanamida; ESMS *m/z* 487.2 ($M + H^+$).

Ejemplo 24

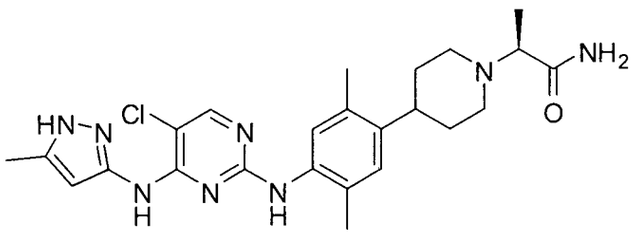
(*S*)-2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-N-metil-propanamida (164)



Una mezcla de la 5-cloro-N^2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (50.0 miligramos, 0.12 milimoles), (*R*)-2-bromo-*N*-metil-propanamida (100.0 miligramos, 0.60 milimoles), y trietil-amina (102.0 microlitros, 0.60 milimoles) en 2 mililitros de dimetil-formamida, se calentó a 150°C en un reactor de microondas durante 30 minutos. La mezcla de reacción se purificó directamente mediante HPLC en fase inversa de preparación, para proporcionar la (*S*)-2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-N-metil-propanamida; ESMS *m/z* 501.2 ($M + H^+$).

Ejemplo 25

(S)-2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-propanamida (166)

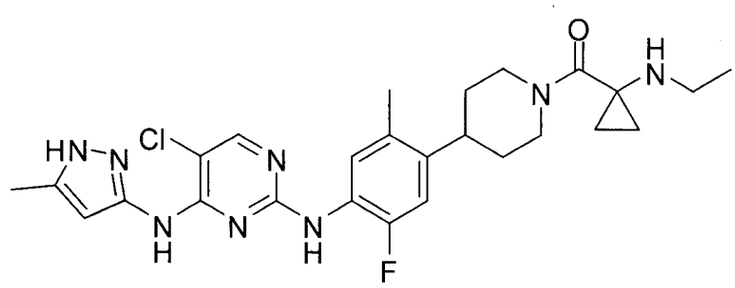


Una mezcla de la 5-cloro-N^2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (50.0 miligramos, 0.12 milimoles), (*R*)-2-bromo-propanamida (90.6 miligramos, 0.60 milimoles), y trietil-amina (102.0 microlitros, 0.60 milimoles) en

2 mililitros de dimetil-formamida, se calentó a 150°C en un reactor de microondas durante 30 minutos. La mezcla de reacción se purificó directamente mediante HPLC en fase inversa de preparación, para proporcionar la (*S*)-2-(4-(4-(5-cloro-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-propanamida; ESMS *m/z* 483.2 ($M + H^+$).

Ejemplo 26

(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-(etil-amino)-ciclopropil)-metanona (169)



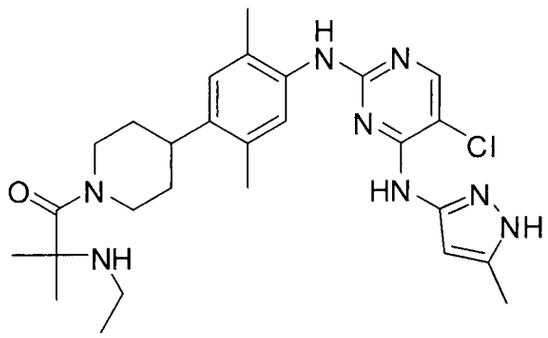
Una mezcla de la 5-cloro-N^2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (67.3 miligramos, 0.17 milimoles), ácido 1-(terbutoxi-carbonil-(etil)-amino)-ciclopropan-carboxílico (38.0 miligramos, 0.17 milimoles), HATU (63.0 miligramos, 0.17 milimoles), y di-isopropil-etil-amina (57 microlitros, 0.34 milimoles) en 1 mililitro de dimetil-formamida se agitó a temperatura ambiente durante la noche. La mezcla de reacción se dividió entre EtOAc y agua, los extractos orgánicos combinados se secaron (Na_2SO_4), y entonces se concentraron al vacío. La mezcla cruda resultante se disolvió en 5 mililitros de

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dicloro-metano y 4 mililitros del ácido trifluoro-acético, y se agitó luego durante 2 horas, seguido por concentración al vacío. El producto crudo se purificó mediante HPLC en fase inversa, para proporcionar la (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-(etil-amino)-ciclopropil)-metanona; ESMS *m/z* 527.2 ($M + H^+$).

Ejemplo 27

1-(4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(etil-amino)-2-metil-propan-1-ona (175)

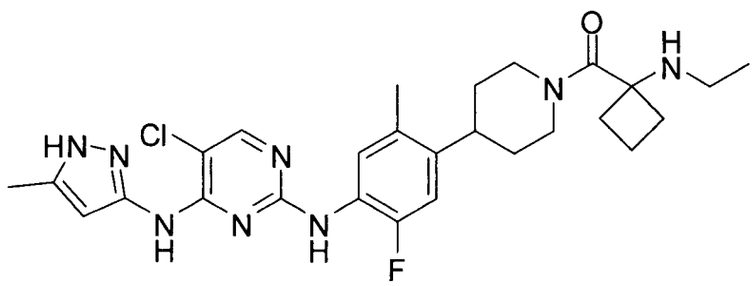


A una solución de la 2-amino-1-(4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-metil-propan-1-ona (6 miligramos, 0.012 milimoles) en acetona (0.5 mililitros), se le agregó K_2CO_3 (11 miligramos, 0.079 milimoles). La mezcla se agitó a temperatura ambiente durante 10 minutos, antes de la adición de EtI (6 miligramos, 0.038 milimoles). La mezcla resultante se agitó luego a temperatura ambiente durante 14 horas antes de tratarse con NH_4Cl acuoso saturado (1 mililitro), y se extrajo con EtOAc (2 mililitros, 3 veces). Las capas orgánicas se

combinaron, se concentraron, y el residuo se purificó mediante cromatografía de capa delgada de preparación (gel de sílice, 8 por ciento de MeOH/DCM/NH_3), seguida por una purificación adicional mediante HPLC en fase inversa de preparación, para proporcionar la 1-(4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(etil-amino)-2-metil-propan-1-ona; ESMS *m/z* 525.3 ($M + H^+$).

Ejemplo 28

(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-(etil-amino)-ciclobutil)-metanona (176)

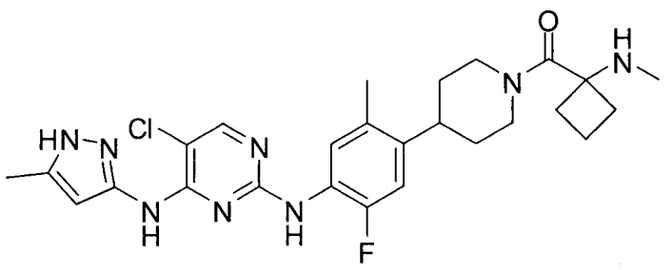


Una mezcla de la 5-cloro-N^2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (50.0 miligramos, 0.12 milimoles), ácido 1-(terbutoxi-carbonil-(etil)-amino)-ciclobutan-carboxílico (29.2 miligramos, 0.12 milimoles), HATU (45.8 miligramos, 0.12 milimoles), y di-isopropil-etil-amina (20 microlitros, 0.12 milimoles) en 1 mililitro de dimetil-formamida se agitó a temperatura ambiente durante la noche. La mezcla de reacción se dividió entre EtOAc y agua. Los extractos orgánicos combinados se secaron (Na_2SO_4), y se concentraron al vacío. La mezcla cruda

resultante se disolvió en 5 mililitros de dicloro-metano y 4 mililitros del ácido trifluoro-acético, y se agitó luego durante 2 horas, seguido por concentración al vacío. El producto crudo se purificó mediante HPLC en fase inversa, para proporcionar la (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-(etil-amino)-ciclobutil)-metanona; ESMS *m/z* 541.3 ($M + H^+$).

Ejemplo 29

(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-(metil-amino)-ciclobutil)-metanona (177)

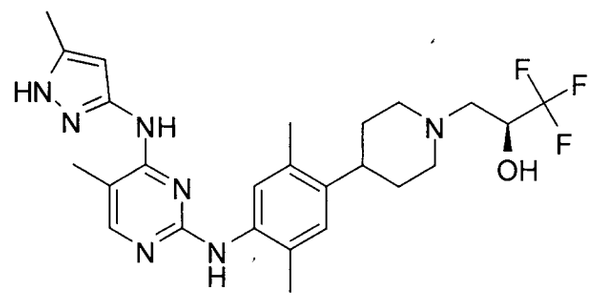


Una mezcla de 5-cloro-N^2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (50.0 miligramos, 0.12 milimoles), ácido 1-(terbutoxi-carbonil-(metil)-amino)-ciclobutan-carboxílico (27.5 0.12 milimoles), HATU (45.8 miligramos, 0.12 milimoles), y di-isopropil-etil-amina (20 microlitros, 0.12 milimoles) en 1 mililitro de dimetil-formamida, se agitó a temperatura ambiente durante la noche. La mezcla de reacción se dividió entre EtOAc y agua. Los extractos orgánicos combinados se secaron (Na_2SO_4), y se concentraron al vacío. La mezcla cruda resultante se

disolvió en 5 mililitros de dicloro-metano y 4 mililitros del ácido trifluoro-acético, y se agitó durante 2 horas, seguido por concentración al vacío. El producto crudo se purificó mediante HPLC en fase inversa, para proporcionar la (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-(metil-amino)-ciclobutil)-metanona; ESMS *m/z* 527.2 ($M + H^+$).

Ejemplo 30

(*S*)-3-(4-(2,5-dimetil-4-(5-metil-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol (179)

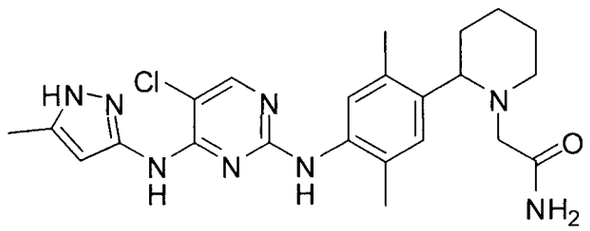


A una solución de clorhidrato de N^2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-5-metil-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (36.0 miligramos, 0.084 milimoles) en N,N-dimetil-formamida (0.5 mililitros) se le agregaron trietil-amina (23.4 microlitros, 0.168 milimoles), y (*S*)-2-(trifluoro-metil)-oxirano (72.8 microlitros, 0.84 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante la noche, y se purificó mediante HPLC en fase inversa de preparación, para proporcionar el (*S*)-3-(4-(2,5-dimetil-4-(5-metil-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-fenil)-piperidin-1-

il)-1,1,1-trifluoro-propan-2-ol; ESMS *m/z* 504.3 ($M + H^+$).

Ejemplo 31

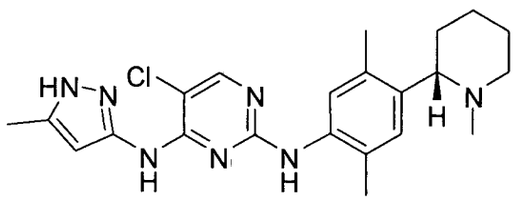
2-(2-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-acetamida (181)



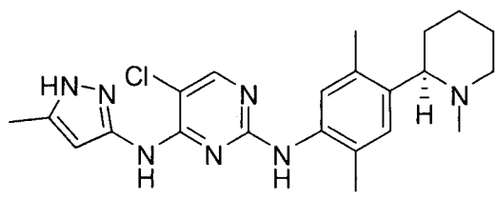
A una mezcla de 5-cloro-N2-(2,5-dimetil-4-(piperidin-2-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (0.12 milimoles), y trietil-amina (83 microlitros, 0.6 milimoles) en N,N-dimetil-formamida (1.5 mililitros), se le agregó 2-bromo-acetamida (35 miligramos, 0.24 milimoles). La mezcla se agitó a temperatura ambiente durante 3 horas. La reacción se filtró, y el filtrado se purificó mediante HPLC en fase inversa, para proporcionar la 2-(2-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-acetamida como un sólido blanco; ^{1}H RMN (400 MHz, MeOD-d4) 8.09 (s, 1H), 7.65 (d, 1H), 7.43 (s, 1H), 6.41 (s, 1H), 4.79-4.74 (m, 2H), 3.83-3.48 (m, 2H), 2.71 (s, 3H), 2.42 (s, 3H), 2.34 (s, 6H), 2.15-1.84 (m, 7H); ESMS *m/z* 469.2 ($M + H^+$).

Ejemplos 32 y 33

(*S*) 5-cloro-N2-(2,5-dimetil-4-(1-metil-piperidin-2-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (183)



(*R*) 5-cloro-N2-(2,5-dimetil-4-(1-metil-piperidin-2-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (184)



Paso 1: A una mezcla de 1-bromo-2,5-dimetil-4-nitro-benceno (185 miligramos, 1 milimol), y 2-(tributil-estanil)-piridina (202 miligramos, 1.1 milimoles) en N,N-dimetil-formamida (4 mililitros), se le agregó tetraquis-(trifenil-fosfina)-paladio(0) (58 miligramos, 0.05 milimoles). El tubo de reacción se selló, la mezcla se purgó con N_2 durante 3 minutos, y entonces se calentó a 120°C bajo N_2 durante la noche. La reacción se enfrió a temperatura ambiente, y se vertió en una solución acuosa saturada de cloruro de amonio. La mezcla de reacción cruda se extrajo con acetato de etilo (15 mililitros, 3 veces). Los extractos orgánicos se combinaron, se lavaron con salmuera, y se concentraron. El producto crudo se purificó mediante cromatografía en gel de sílice (acetato de etilo al 60 por ciento en hexanos), para proporcionar la 2-(2,5-dimetil-4-nitro-fenil)-piridina como un sólido blanco. El sólido obtenido se disolvió en ácido acético/ácido trifluoro-acético (15 mililitros/200 microlitros). A esta solución se le agregó PtO_2 (al 10 por ciento en peso/peso). La

mezcla de reacción se desgasificó y se purgó con H_2 varias veces y entonces se agitó vigorosamente bajo 1 atmósfera de H_2 durante la noche. La mezcla se filtró, y el filtrado se concentró, para proporcionar la 2,5-dimetil-4-(piperidin-2-il)-anilina como un aceite color amarillo; ESMS *m/z* 205 ($M + H^+$).

Paso 2: Una mezcla de la 2,5-dicloro-N-(5-metil-1H-pirazol-3-il)-pirimidin-4-amina (120 miligramos, 0.49 milimoles), y 2,5-dimetil-4-(piperidin-2-il)-anilina (100 miligramos, 0.49 milimoles) en 2-propanol (10 mililitros) se trató con HCl acuoso concentrado (7 gotas). La mezcla se selló y se calentó en un reactor de microondas a 130°C durante 45 minutos. La mezcla se concentró, para proporcionar la 5-cloro-N2-(2,5-dimetil-4-(piperidin-2-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina; ESMS *m/z* 412.1 ($M + H^+$). El producto crudo se utilizó directamente para el siguiente paso sin mayor purificación.

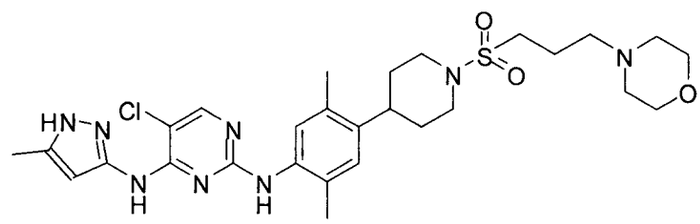
Paso 3: A una solución del producto crudo a partir del paso anterior en tetrahidrofurano (1 mililitro) y metanol (1 mililitro), se le agregaron en secuencia formaldehído (100 microlitros, 1.3 milimoles) y 5 gotas de AcOH. La mezcla de reacción se agitó a temperatura ambiente durante 1 hora, y entonces se agregó ciano-borohidruro de sodio (160 miligramos, 2.45 milimoles) en una porción, y la reacción se agitó durante 30 minutos adicionales. La reacción se apagó con NH_4Cl acuoso saturado y se concentró al vacío, para dar un residuo oleoso. El residuo se purificó mediante HPLC en fase inversa, para proporcionar la (±)-5-cloro-N2-(2,5-dimetil-4-(1-metil-piperidin-2-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un

sólido blanco; ESMS *m/z* 426.2 ($M + H^+$).

Paso 4: La separación quiral de la mezcla racémica se condujo mediante HPLC en fase normal utilizando una columna ChiralPaK AD-H empleando el siguiente sistema de solventes: hexanos (95 por ciento), EtOH (2.5 por ciento), metanol (2.5 por ciento). Los dos picos de los enantiómeros purificados se recolectaron por separado: (*R*)-5-cloro-N2-(2,5-dimetil-4-(1-metil-piperidin-2-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina y (*S*)-5-cloro-N2-(2,5-dimetil-4-(1-metil-piperidin-2-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina; ambos picos: ESMS *m/z* 426.2 ($M + H^+$). El pico de elución más temprana se asignó arbitrariamente como el enantiómero (*R*).

Ejemplo 34

5-cloro-N^2-(2,5-dimetil-4-(1-(3-morfolinopropil-sulfonil)-piperidin-4-il)-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina (194)



Paso 1: A una solución de la 5-cloro-N^2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina (78 miligramos, 0.19 milimoles), y trietil-amina (0.52 mililitros, 3.78 milimoles) en dicloro-metano (10 mililitros), se le agregó cloruro de 3-cloropropan-1-sulfonilo (63 miligramos, 0.36 milimoles, en 1 mililitro de dicloro-metano). Después de agitar a temperatura

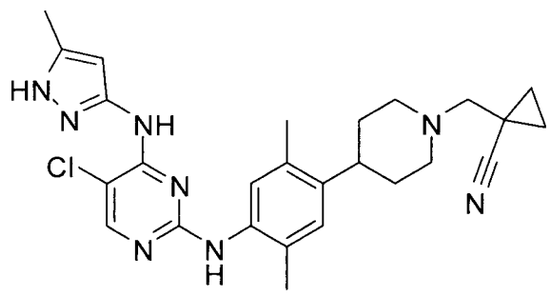
ambiente durante una hora, se agregó EtOAc (100 mililitros). La mezcla se lavó en secuencia con agua (10 mililitros), salmuera (10 mililitros), se secó sobre Na_2SO_4 y se concentró al vacío. El producto crudo se purificó mediante cromatografía en gel de sílice (gradiente del 0 al 100 por ciento de EtOAc en hexanos), para dar la 5-cloro-N2-(4-(1-(3-cloropropil-sulfonil)-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un sólido grisáceo; ESMS m/z 552.2 ($M+H^+$).

Paso 2: El producto a partir del paso 1 se agitó en morfolina pura (0.5 mililitros) a 100°C en un frasco sellado durante una hora. La reacción se purificó mediante HPLC en fase inversa, para dar la 5-cloro-N2-(2,5-dimetil-4-(1-(3-morfolinopropil-sulfonil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un polvo blanco; ESMS m/z 603.2 ($M+H^+$).

Ejemplo 35

1-((4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-metil)-ciclopropan-carbonitrilo

(198)

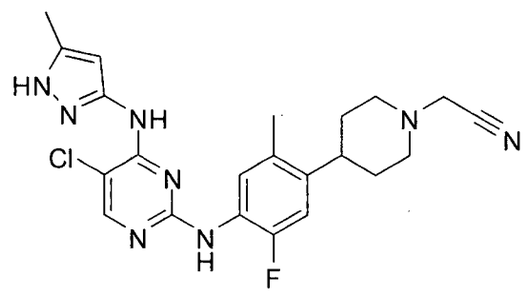


A una solución de la 5-cloro-N^2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina (30 mili-

gramos, 0.078 milimoles) en acetonitrilo (1.0 mililitros), se le agregó 4-metil-bencen-sulfonato de (1-ciano-ciclopropil)-metilo (16 miligramos, 0.10 milimoles, se preparó de acuerdo con el procedimiento descrito en la Publicación Internacional Número WO2005063247), seguido por DIEA (30 miligramos, 0.23 milimoles), y KI (cantidad catalítica). La mezcla resultante se calentó a 70°C durante 14 horas, y entonces se enfrió a temperatura ambiente. La mezcla resultante se purificó directamente mediante HPLC en fase inversa de preparación, para proporcionar el 1-((4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5dimetil-fenil)-piperidin-1-il)-metil)-ciclopropan-carbonitrilo; ESMS *m/z* 491.2 ($M + H^+$).

Ejemplo 36

2-(4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-acetonitrilo (199)

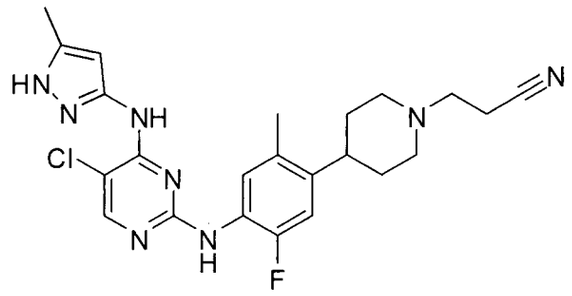


A una solución de 5-cloro-N^2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina (20 miligramos, 0.048 milimoles) en acetonitrilo (0.5 mililitros), se le agregaron Cs_2CO_3 (31 miligramos, 0.096 milimoles), y cloro-acetonitrilo (7 miligramos, 0.096 milimoles). La mezcla resultante se agitó a temperatura ambiente durante 14 horas antes de tratarse con

NH_4Cl acuoso saturado (1 mililitro), y se extrajo con EtOAc (2 mililitros, 3 veces). Las capas orgánicas se combinaron, se concentraron, y el residuo se purificó mediante HPLC en fase inversa de preparación, para proporcionar el 2-(4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-acetonitrilo; ESMS *m/z* 455.2 ($M + H^+$).

Ejemplo 37

3-(4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propano-nitrilo (200)

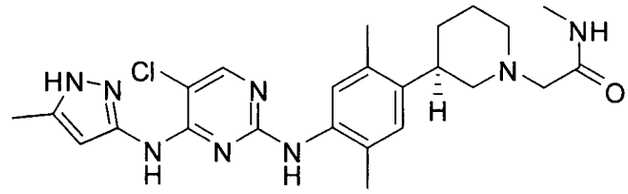


A una solución de la 5-cloro-N^2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina (20 miligramos, 0.048 milimoles) en metanol (0.5 mililitros), se le agregó acrilonitrilo (5 miligramos, 0.096 milimoles). La mezcla resultante se agitó a temperatura ambiente durante 14 horas, y entonces se purificó directamente mediante HPLC en fase inversa de preparación, para proporcionar el 3-(4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propano-nitrilo; ESMS *m/z* 469.2 ($M + H^+$).

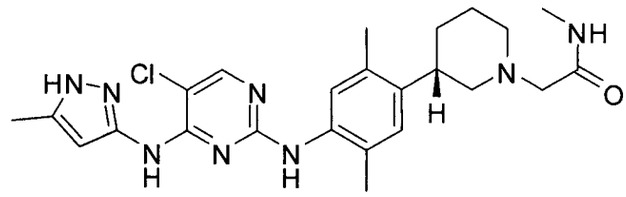
Ejemplos 38 y 39

(*R*)-2-(3-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-

amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida (207)



(*S*)-2-(3-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida (208)

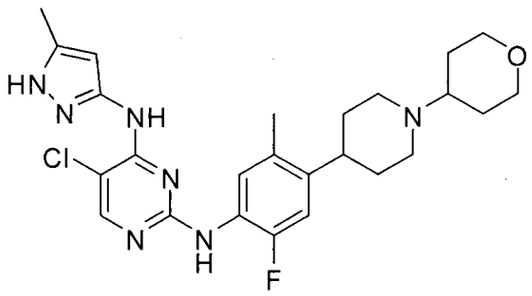


Una solución de 5-cloro-N^2-(2,5-dimetil-4-(piperidin-3-il)-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina (700 miligramos, 1.70 milimoles), 2-bromo-*N*-metil-acetamida (258 miligramos, 1.70 milimoles), y trietil-amina (1.2 mililitros, 8.5 milimoles) en N,N-dimetil-formamida (4 mililitros) se agitó a temperatura ambiente durante 30 minutos. La reacción se purificó mediante HPLC en fase inversa, para dar el producto como un racemato; ESMS m/z 483.2 (M+1). La separación quiral de la mezcla racémica se condujo con HPLC quiral (ChiralCel OD-H, Hex:EtOH:MeOH/80:10:10, tiempo de ejecución de 15 minutos, 1 mililitro/minuto). Los dos picos de los enantiómeros purificados se recolectaron por separado, ambos como sólidos blancos: (*R*)-2-(3-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida y (*S*)-2-(3-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-

acetamida; ambos picos: ESMS *m/z* 483.2 ($M+H^+$). El pico de elución más temprana (rt = 5.63 minutos. contra rt = 7.62 minutos.) se asignó arbitrariamente como el enantiómero (*R*).

Ejemplo 40

5-cloro-N^2-(2-fluoro-5-metil-4-(1-(tetrahidro-2H-piran-4-il)-piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (209)

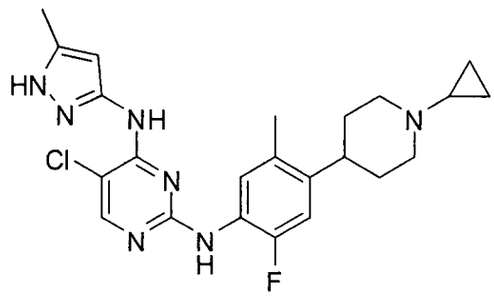


A una suspensión de 5-cloro-N^2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (2.50 gramos, 6.0 milimoles) en un solvente mixto de metanol (42 mililitros), y dicloro-metano (10 mililitros), se le agregó dihidro-2H-piran-4(3H)-ona (3.33 mililitros, 36.0 milimoles), y trietil-amina (8.36 mililitros, 60.0 milimoles). La mezcla de reacción se calentó a 60°C durante 1 hora antes de agregar $NaCNBH_3$ (1.66 gramos, 26.4 milimoles). La mezcla se calentó a 60°C durante otras 2 horas, se enfrió a temperatura ambiente, se diluyó con dicloro-metano (60 mililitros), se cargó en seco sobre gel de sílice (12.5 gramos), y se purificó mediante cromatografía en gel de sílice (gradiente de dicloro-metano con el 1 por ciento de NH_3 hasta el 10 por ciento de metanol en dicloro-metano con el 1 por ciento de NH_3), para proporcionar la 5-cloro-N2-(2-fluoro-5-metil-4-(1-(tetrahidro-2H-piran-

4-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un sólido blanco; ^{1}H RMN (DMSO-d_6, 400 MHz) δ 12.08 (br, 1H), 9.58 (br, 1H), 8.65 (d, J = 28.4 Hz, 1H), 8.02 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 12.4 Hz, 1H), 6.08 (br, 1H), 3.89 (dd, J = 10.8, 3.6 Hz, 2H), 3.28 (t, J = 10.4 Hz, 2H), 2.99 (d, J = 10.8 Hz, 2H), 2.64-2.43 (m, 2H), 2.24-2.15 (m, 8H), 1.71-1.40 (m, 8H); ESMS m/z 500.2 (M + H$^+$).

Ejemplo 41

5-cloro-N^2-(4-(1-ciclopropil-piperidin-4-il)-2-fluoro-5-metil-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina (210)

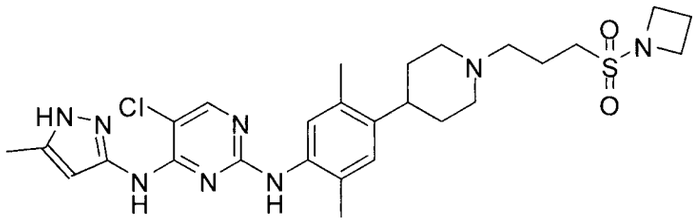


A una solución de la 5-cloro-N^2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina (30 miligramos, 0.072 milimoles) en metanol (0.7 mililitros), se le agregaron AcOH (35 miligramos, 0.58 milimoles), (1-etoxi-ciclopropoxi)-trimetil-silano (37 miligramos, 0.216 milimoles), y una pequeña cantidad de tamices moleculares de 4 Angstroms. La mezcla se agitó a temperatura ambiente durante 1 hora antes de la adición de Na(CN)BH$_3$ (14 miligramos, 0.216 milimoles). La mezcla resultante entonces se agitó a 60°C durante 14 horas, y se enfrió a temperatura ambiente. Se agregó NH$_4$Cl acuoso saturado (2 mililitros), y la

mezcla se extrajo con EtOAc (3 mililitros, 3 veces). Las capas orgánicas combinadas se concentraron y se purificaron mediante HPLC en fase inversa de preparación, para proporcionar la 5-cloro-N^2-(4-(1-ciclopropil-piperidin-4-il)-2-fluoro-5-metil-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina; ^{1}H RMN (400 MHz, MeOD-d4) δ 7.97 (s, 1H), 7.84 (d, 1H), 7.50 (s, 1H), 6.93 (d, 1H), 6.29 (s, 1H), 5.33 (s, 1H), 2.80 (m, 1H), 2.58 (s, 2H), 2.28 (s, 3H), 2.24 (s, 3H), 1.96 (m, 1H), 1.80-1.85(m, 2H), 1.65-1.75 (m, 2H), 0.2-0.7 (m, 6H); ESMS *m/z* 456.2 ($M + H^+$).

Ejemplo 42

N^2-(4-(1-(3-(azetidin-1-il-sulfonil)-propil)-piperidin-4-il)-2,5-dimetil-fenil)-5-cloro-*N*^{4}-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (214)

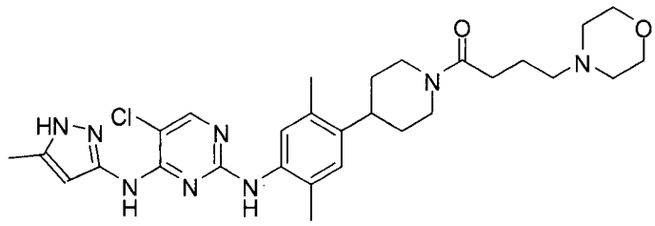


Paso 1: A una solución de azetidina (12 miligramos, 0.21 milimoles), y trietil-amina (0.1 mililitros, 0.71 milimoles) en dicloro-metano (5 mililitros), se le agregó lentamente una solución de cloruro de 3-cloropropan-1-sulfonilo (34 miligramos, 0.19 milimoles) en dicloro-metano (1 mililitro). Después de agitar a temperatura ambiente durante la noche, el solvente se removió al vacío. El producto crudo de 1-(3-cloropropil-sulfonil)-azetidina resultante se disolvió en NMP (1.9 mililitros, 0.1 milimoles/mililitro), y se utilizó en el siguiente paso sin mayor purificación; ESMS m/z 198.0 ($M+H^+$).

Paso 2: Una mezcla de la 5-cloro-N^2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (42 miligramos, 0.1 milimoles), 1-(3-cloropropil-sulfonil)-azetidina (paso 1, 0.1 milimoles), trietil-amina (70 microlitros), y yoduro de sodio (150 miligramos) en NMP (1 mililitro), se colocó en un frasco sellado, el cual se calentó en un reactor de microondas durante 30 minutos a 150°C. La reacción se purificó mediante HPLC en fase inversa, para dar la N2-(4-(1-(3-(azetidin-1-il-sulfonil)-propil)-piperidin-4-il)-2,5-dimetil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un polvo blanco; ESMS m/z 573.3 ($M+H^+$).

Ejemplo 43

1-(4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-4-morfolinobutan-1-ona (224)



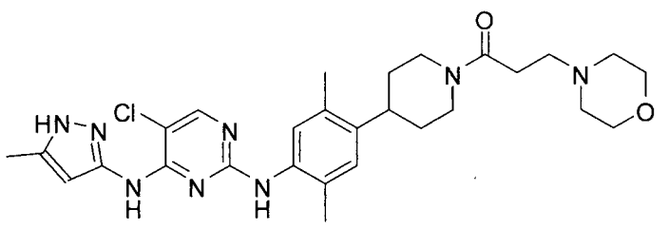
Paso 1: A una solución de HATU (95 miligramos, 0.255 milimoles), y ácido 4-cloro-butanoico (36 miligramos, 0.25 milimoles) en N,N-dimetil-formamida (1 mililitro), se le agregó DIEA (0.1 mililitros). Después de agitar a temperatura ambiente durante 3 minutos, se agregó 5-cloro-N^2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina (100 miligramos, 0.24

milimoles) en N,N-dimetil-formamida (2 mililitros). La reacción se agitó a temperatura ambiente durante 90 minutos, en cuyo punto la LCMS indicó que la reacción estaba completa, y que se había generado la 4-cloro-1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-butan-1-ona; ESMS m/z 516.1($M+H^+$).

Paso 2: Se agregó morfolina (0.5 mililitros) directamente a la mezcla de reacción cruda a partir del paso 1 (1 mililitro). La solución resultante se agitó a 100°C en un frasco sellado durante 1.5 horas. El producto crudo se purificó mediante HPLC en fase inversa, para dar la 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-4-morfolinobutan-1-ona como un polvo blanco; ESMS m/z 567.3 ($M+H^+$).

Ejemplo 44

1-(4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-3-morfolino-propan-1-ona (225)



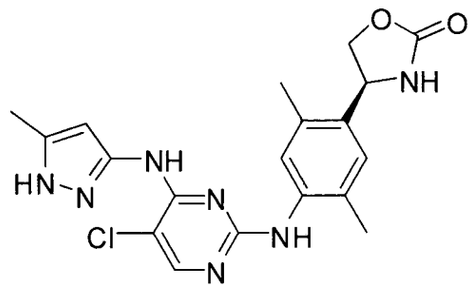
Paso 1: Una solución de HATU (108 miligramos, 0.28 milimoles), ácido 3-cloro-propanoico (30 miligramos, 0.28 milimoles), y DIEA

(0.1 mililitros) en N,N-dimetil-formamida (1 mililitro) se agitó a temperatura ambiente. Después de 3 minutos, esta solución se transfirió a una solución de 5-cloro-N^2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (111 miligramos, 0.27 milimoles) en N,N-dimetil-formamida (10 mililitros). La mezcla resultante se agitó a temperatura ambiente durante la noche. La reacción se apagó con agua (20 mililitros), y se extrajo con EtOAc (30 mililitros, 3 veces). Las capas de EtOAc combinadas se lavaron con salmuera (10 mililitros), se secaron sobre Na_2SO_4 y se concentraron al vacío. El producto crudo se purificó mediante cromatografía en gel de sílice (gradiente del 0 al 10 por ciento de metanol en dicloro-metano con aditivo de NH_3 al 1 por ciento), para dar la 1-(4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-prop-2-en-1-ona como un aceite color café claro; ESMS m/z 466.1 ($M+H^+$).

Paso 2: Una solución de 1-(4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-prop-2-en-1-ona (41 miligramos, 0.88 milimoles), y morfolina (0.1 mililitros) en N,N-dimetil-formamida (1 mililitro) se agitó a temperatura ambiente durante la noche. El producto crudo se purificó mediante HPLC en fase inversa, para dar la 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-3-morfolino-propan-1-ona como un polvo blanco; ESMS m/z 553.2 ($M+H^+$).

Ejemplo 45

(S)-4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-oxazolidin-2-ona (230)



Paso 1: A un recipiente de reacción para microondas se le agregó una mezcla de 1-bromo-2,5-dimetil-4-nitro-benceno (1.15 gramos, 5.0 milimoles), boronato de dibutil-vinilo (1.16 gramos, 6.3 milimoles), $Pd(PPh_3)_4$ (289 miligramos, 0.25 milimoles), CsF (2.28 gramos, 15 milimoles), y un solvente mixto (1,2-dimetoxi-etano/MeOH=2:1, 15 mililitros). La mezcla se desgasificó y se selló con N_2. El recipiente de reacción entonces se calentó a 130°C en un reactor de microondas durante 15 minutos. Después de abrir el recipiente de reacción, la mezcla se vertió en una solución acuosa saturada de NH_4Cl (30 mililitros), y se extrajo con EtOAc (50 mililitros, 3 veces). Las capas orgánicas combinadas se lavaron con salmuera, y se secaron ($MgSO_4$). Después de remover el agente de secado mediante filtración, el filtrado se concentró y se purificó mediante cromatografía en columna por evaporación instantánea (gel de sílice, gradiente del 0 al 30 por ciento de EtOAc en hexanos), para proporcionar el 1,4-dimetil-2-nitro-5-vinil-benceno como cristales en forma de agujas; ESMS *m/z* 178.1 ($M + H^+$).

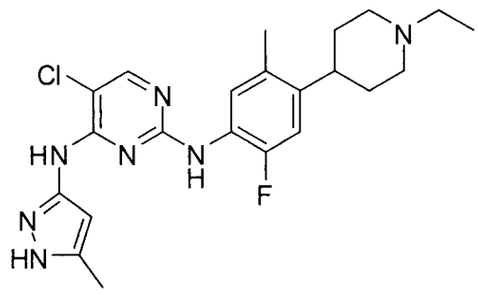
Paso 2: El 1,4-dimetil-2-nitro-5-vinil-benceno se hizo reaccionar por medio del método sintético asimétrico reportado por N. Barta y colaboradores, (*Org. Lett.* **2000**, *2*, 2821), seguido por purificación con HPLC en fase inversa de preparación, para proporcionar la (*S*)-4-(2,5-dimetil-4-nitro-fenil)-oxazolidin-2-ona; ESMS *m/z* 237.1 ($M+H^+$).

Paso 3: A una solución de la (*S*)-4-(2,5-dimetil-4-nitro-fenil)-oxazolidin-2-ona (55 miligramos, 0.23 milimoles) en metanol (5 mililitros), se le agregó Pd/C (5 miligramos, 10 por ciento en peso/peso). La mezcla se desgasificó y se agitó a temperatura ambiente bajo 1 atmósfera de H_2 durante 14 horas. El Pd/C se removió mediante filtración a través de Celite. El filtrado se concentró, para proporcionar la (*S*)-4-(4-amino-2,5-dimetil-fenil)-oxazolidin-2-ona, la cual se utilizó en el siguiente paso sin mayor purificación; ESMS *m/z* 207.1 ($M + H^+$).

Paso 4: A un tubo de reacción se le agregaron (*S*)-4-(4-amino-2,5-dimetil-fenil)-oxazolidin-2-ona (48 miligramos, 0.23 milimoles), 2,5-dicloro-N-(5-metil-1*H*-pirazol-3-il)-pirimidin-4-amina (77 miligramos, 0.32 milimoles), ^{i}PrOH (2 mililitros), y HCl (0.13 mililitros, 0.52 milimoles, 4N en dioxano). El tubo entonces se selló y se calentó a 130°C durante 6 horas. Después de enfriarse a temperatura ambiente, la mezcla se concentró y se purificó mediante HPLC en fase inversa de preparación, para proporcionar la (*S*)-4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-oxazolidin-2-ona; ESMS *m/z* 414.1 ($M + H^+$).

Ejemplo 46

5-cloro-N^2-(4-(1-etil-piperidin-4-il)-2-fluoro-5-metil-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (232)

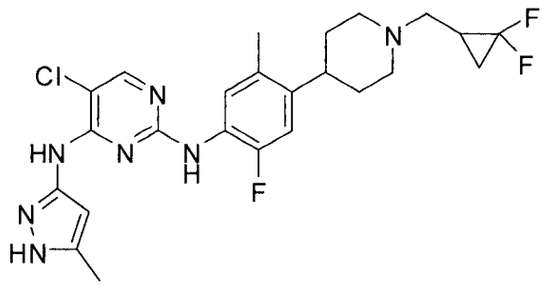


Una mezcla de la 5-cloro-N^2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (400 miligramos, 0.96 milimoles), yodo-etano (92.5 microlitros, 1.2 milimoles), y trietil-amina (201.5 microlitros, 1.4 milimoles) en 4 mililitros de dimetil-formamida se calentó a 60°C durante 2 horas. La mezcla de reacción se dividió entre EtOAc y agua. Los extractos orgánicos combinados se secaron (Na_2SO_4), y se concentraron al vacío. El producto crudo se purificó mediante cromatografía en gel de sílice (MeOH/DCM: 1/9), para proporcionar la 5-cloro-N^2-(4-(1-etil-piperidin-4-il)-2-fluoro-5-metil-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina; ^{1}H RMN (DMSO-d_6) δ 8.01 (s, 1H), 7.35 (m, 1H), 7.02 (d, 1H), 6.22 (s,1H), 2.97 (d, 2H), 2.62 (m, 1H), 2.34 (q, 2H), 2.21 (s, 3H), 2.13 (s, 3H), 1.98 (t, 2H), 1.64 (m, 4H), 1.01 (t, 3H); ESMS *m/z* 444.2 (M + H^+).

Ejemplo 47

5-cloro-N^2-(4-(1-((2,2-difluorociclopropil)-metil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

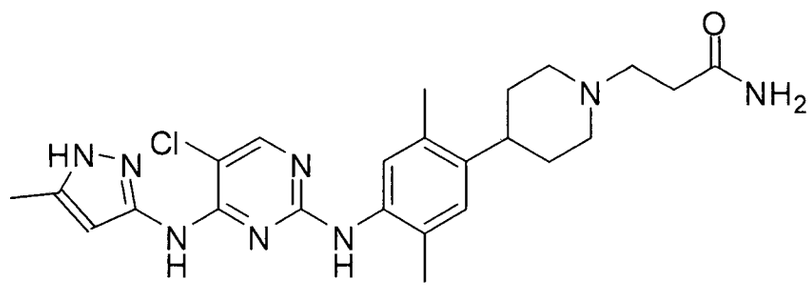
(235)



Una mezcla de la 5-cloro-N^2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (40 miligramos, 0.096 milimoles), 2-(bromo-metil)-1,1-difluoro-ciclopropano (32.8 miligramos, 0.19 milimoles), y trietil-amina (20.2 microlitros, 0.14 milimoles) en 1 mililitro de dimetil-formamida, se calentó a 150°C en un reactor de microondas durante 30 minutos. El producto crudo se purificó mediante HPLC en fase inversa, para proporcionar la 5-cloro-N^2-(4-(1-((2,2-difluorociclopropil)-metil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina; ESMS *m/z* 506.2 ($M + H^+$).

Ejemplo 48

3-(4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-propanamida (236)



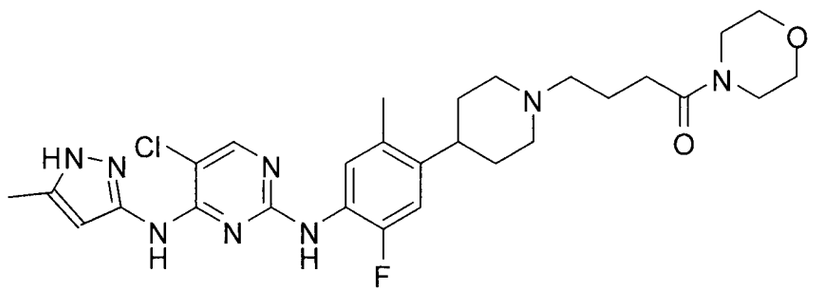
Una solución de 5-cloro-N^2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-

N^4-(5-metil-*1H*-pirazol-3-il)-pirimidin-2,4-diamina (41 miligramos, 0.1 milimoles), acrilamida (24 miligramos, 0.33 milimoles), y DIEA (87 microlitros, 0.5 milimoles) en NMP (1 mililitro) se agitó a 80°C durante 10 horas. La LCMS en este punto mostró que la reacción no estaba completa, de modo que se agregó acrilamida adicional (36 miligramos, 2 veces), y la reacción se continuó hasta que la LCMS mostró que la reacción estaba completa. El producto crudo se purificó mediante HPLC en fase inversa, para dar la 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-propanamida como un polvo blanco; ESMS m/z 483.2 (M+1).

Ejemplo 49

4-(4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-1-morfolinobutan-1-ona

(246)

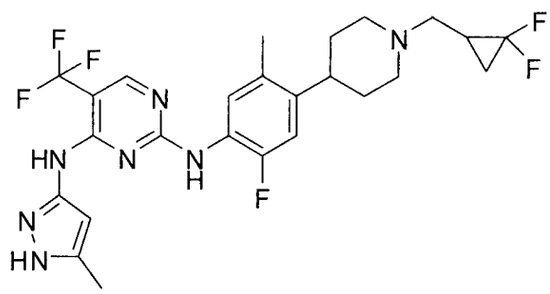


Una mezcla de 5-cloro-N^2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina (41 miligramos, 0.1 milimoles), 4-cloro-1-morfolino-butan-1-ona (29 miligramos, 0.15 milimoles), y DIEA (0.1 mililitros, 0.58 milimoles) en NMP (1 mililitro) se agitó a 80°C. Después de 10 horas, se agregó 4-

cloro-1-morfolinobutan-1-ona adicional (51 miligramos), y la reacción se continuó durante la noche. El producto crudo se purificó mediante HPLC en fase inversa, para dar la 4-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-1-morfolinobutan-1-ona como un polvo blanco; ESMS m/z 571.3.3 ($M+H^+$).

Ejemplo 50

N^2-(4-(1-((2,2-difluorociclopropil)-metil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N^4-(5-metil-1H-pirazol-3-il)-5-(trifluoro-metil)-pirimidin-2,4-diamina (251)

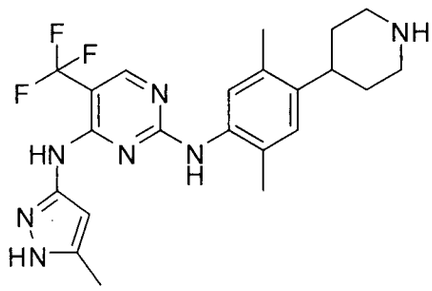


Una mezcla de la N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-5-(trifluoro-metil)-pirimidin-2,4-diamina (100 miligramos, 0.22 milimoles), 2-(bromo-metil)-1,1-difluoro-ciclopropano (76.4 miligramos, 0.45 milimoles), y trietil-amina (60.6 microlitros, 0.42 milimoles) en 1 mililitro de dimetil-formamida, se calentó a 60°C en un reactor de microondas durante 2 horas. El producto crudo se purificó mediante HPLC en fase inversa, para proporcionar la N^2-(4-(1-((2,2-difluoro-ciclopropil)-metil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N^4-(5-metil-1H-pirazol-3-il)-5-(trifluoro-metil)-pirimidin-2,4-diamina; ESMS *m/z* 540.2 ($M + H^+$).

202

Ejemplo 51

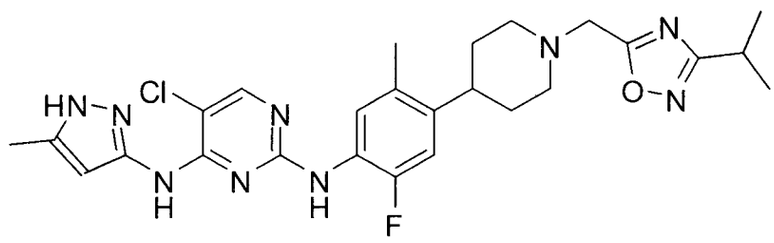
N^{2-}(2,5-dimetil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-5-(trifluoro-metil)-pirimidin-2,4-diamina (257)



Una mezcla de la 2-cloro-N-(5-metil-1H-pirazol-3-il)-5-(trifluoro-metil)-pirimidin-4-amina (513.0 miligramos, 0.9 milimoles), 4-(4-amino-2,5-dimetil-fenil)-piperidin-1-carboxilato de terbutilo (282.7 miligramos, 0.9 milimoles), y HCl acuoso concentrado (10 gotas) en *i*-PrOH (12 mililitros) se calentó a 150°C en un reactor de microondas durante 30 minutos. El producto crudo se purificó mediante HPLC en fase inversa, para proporcionar la N^{2-}(2,5-dimetil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-5-(trifluoro-metil)-pirimidin-2,4-diamina; ESMS *m/z* 446.2 ($M + H^+$).

Ejemplo 52

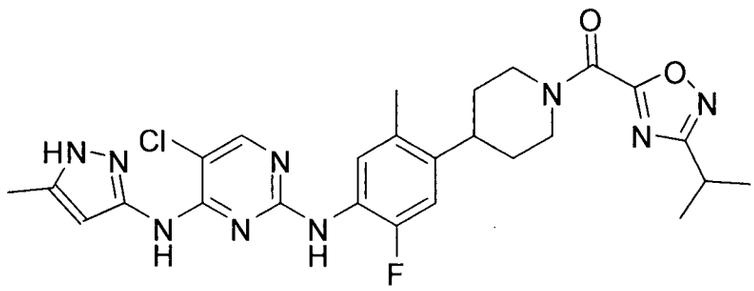
5-cloro-N^2-(2-fluoro-4-(1-((3-isopropil-1,2,4-oxadiazol-5-il)-metil)-piperidin-4-il)-5-metil-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina (259)



Una mezcla de la 5-cloro-N^2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina (42 miligramos, 0.1 milimoles), 5-(cloro-metil)-3-isopropil-1,2,4-oxadiazol (17 miligramos, 0.10 milimoles), y DIEA (86 microlitros, 0.5 milimoles) en N,N-dimetil-formamida (1 mililitro) se agitó a temperatura ambiente durante la noche. La reacción se diluyó con EtOAc (50 mililitros), y se lavó con agua (5 mililitros, 2 veces). La capa de EtOAc se secó sobre Na_2SO_4 y se concentró al vacío. El producto crudo se purificó mediante cromatografía en gel de sílice (gradiente del 50 al 100 por ciento de EtOAc en hexanos), para dar la 5-cloro-N2-(2-fluoro-4-(1-((3-isopropil-1,2,4-oxadiazol-5-il)-metil)-piperidin-4-il)-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un sólido blanco; ESMS m/z 540.2 ($M+H^+$).

Ejemplo 53

(4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(3-isopropil-1,2,4-oxadiazol-5-il)-metanona (265)



Paso 1: Una solución de isobutironitrilo (4.49 mililitros, 50 milimoles) e hidroxilamina (12.3 mililitros, 200 milimoles) en etanol anhidro (20 mililitros) se agitó a 60°C durante dos días. El solvente

se evaporó. El residuo se co-evaporó repetidamente con tolueno, para dar la (*E*)-*N*'-hidroxi-isobutirimidamida como un líquido amarillo claro; ^{1}H RMN (400 MHz, $CDCl_3$) δ 7.50 (br s, 1H), 4.52 (br s, 2H), 2.43 (septeto, *J* = 6.8 Hz, 1H), 1.15 (d, *J* = 6.8 Hz, 6H).

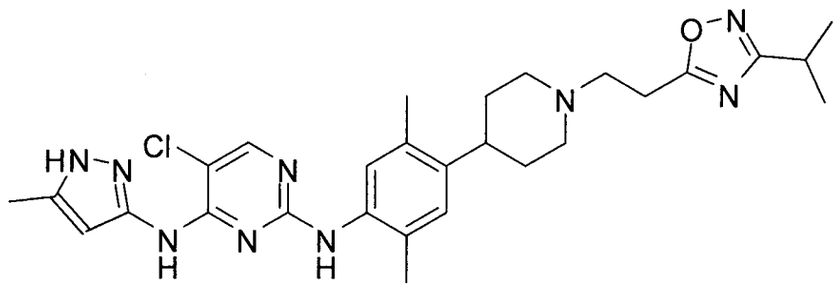
Paso 2: Una solución de la (*E*)-*N*'-hidroxi-isobutirimidamida (0.51 gramos, 5 milimoles), y anhídrido tricloro-acético (2.31 gramos, 7.5 milimoles) en tolueno (20 mililitros) se agitó a 80°C. Después de 4 horas, la reacción se diluyó con EtOAc (50 mililitros), se lavó con $NaHCO_3$ acuoso saturado (10 mililitros, 2 veces), se secó sobre Na_2SO_4 y se evaporó, para dar el 3-isopropil-5-(tricloro-metil)-1,2,4-oxadiazol como un líquido transparente, el cual se utilizó sin mayor purificación; ^{1}H RMN (400 MHz, $CDCl_3$) δ 3.16 (septeto, *J* = 7.2 Hz, 1H), 1.39 (d, *J* = 6.8 Hz, 6H).

Paso 3: Una mezcla de la 5-cloro-N^2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (42 miligramos, 0.1 milimoles), 3-isopropil-5-(tricloro-metil)-1,2,4-oxadiazol (46 miligramos, 0.2 milimoles), y DIEA (40 microlitros, 0.23 milimoles) en metanol (1 mililitro) se agitó a 70°C durante la noche. La mezcla de reacción cruda se purificó mediante HPLC en fase inversa, para dar la (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(3-isopropil-1,2,4-oxadiazol-5-il)-metanona como un sólido blanco; ^{1}H RMN (400 MHz, $CDCl_3$) δ 9.67 (br s, 2H), 8.50 (s, 1H), 8.07 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 12.4 Hz, 1H), 6.16 (s, 1H), 5.53 (s, 1H), 3.98 (d, *J* = 13.2 Hz, 1H), 3.34 (dt, *J* = 2.0, 2.8 Hz, 1H), 3.15 (m, 1H),

2.82 (m, 2H), 2.62 (t, *J* = 4.8 Hz, 2H), 2.34 (s, 3H), 2.25 9s, 3H), 1.90 (m, 2H), 1.76 (2 H); ESMS *m/z* 554.2 ($M+H^+$).

Ejemplo 54

5-cloro-N_2-(4-(1-(2-(3-isopropil-1,2,4-oxadiazol-5-il)-etil)-piperidin-4-il)-2,5-dimetil-fenil)-N_4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (269)



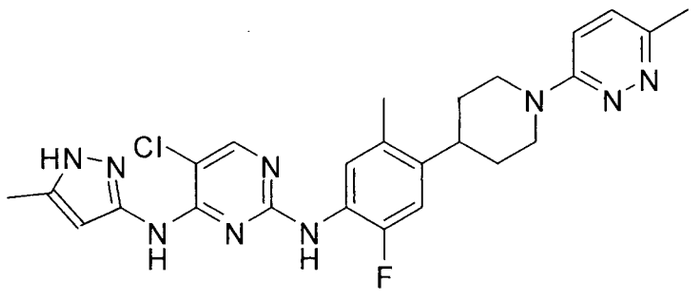
Paso 1: Una mezcla de la (*E*)-*N*'-hidroxi-isobutirimidamida (510 miligramos, 5 milimoles), ácido 3-cloro-propanoico (542 miligramos, 5 milimoles), y diciclohexil-carbodi-imida (1.24 gramos, 6 milimoles) en dioxano anhidro (20 mililitros), se agitó a 0°C durante 1 hora, y luego a temperatura ambiente durante 1 hora adicional. La reacción entonces se calentó a 80°C durante 18 horas adicionales. La reacción se filtró, y el filtrado se evaporó. El residuo resultante se purificó mediante cromatografía en gel de sílice (gradiente del 0 al 100 por ciento de EtOAc en hexanos), para dar el 5-(2-cloro-etil)-3-isopropil-1,2,4-oxadiazol; ^1H RMN (400 MHz, $CDCl_3$) δ 3.85 (t, *J* = 7.2 Hz, 2H), 3.27 (t, *J* = 7.2 Hz, 2H), 3.03 (septeto, *J* = 7.2 Hz, 1H), 1.13 (d, *J* = 7.2 Hz, 6H); ESMS *m/z* 175.1 ($M+H^+$).

Paso 2: Una mezcla de la 5-cloro-N_2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-N_4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina (14 mili-

gramos, 0.033 milimoles), 5-(2-cloro-etil)-3-isopropil-1,2,4-oxadiazol (9 miligramos, 0.053 milimoles), y DIEA (29 microlitros, 0.17 milimoles) en NMP (1 mililitro), se agitó a 50°C durante 3 días. La mezcla de reacción cruda se purificó mediante HPLC en fase inversa, para dar la 5-cloro-N2-(4-(1-(2-(3-isopropil-1,2,4-oxadiazol-5-il)-etil)-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un sólido blanco; ESMS *m/z* 550.3 ($M+H^+$).

Ejemplo 55

5-cloro-N_2-(2-fluoro-5-metil-4-(1-(6-metil-piridazin-3-il)-piperidin-4-il)-fenil)-N_4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina (277)

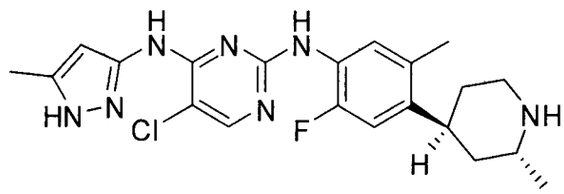


Una suspensión de la 5-cloro-N^2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (20 miligramos, 0.05 milimoles), 3-cloro-6-metil-piridazina (13 miligramos, 0.1 milimoles), y Cs_2CO_3 (33 miligramos, 0.1 milimoles) en dioxano (1 mililitro), se agitó a 150°C en un frasco sellado. Después de 15 horas, se agregaron 3-cloro-6-metil-piridazina (26 miligramos), y Cs_2CO_3 (66 miligramos) adicionales. La reacción se continuó durante 3 horas adicionales. La mezcla de reacción cruda se purificó mediante HPLC en fase inversa, para dar la 5-cloro-N2-(2-fluoro-5-metil-4-(1-(6-metil-piridazin-3-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-

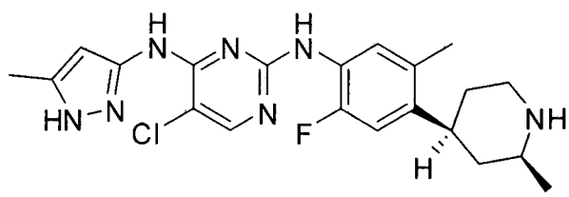
pirazol-3-il)-pirimidin-2,4-diamina como un sólido blanco; ESMS *m/z* 508.2 ($M+H^+$).

Ejemplos 56 y 57

5-cloro-N2-(2-fluoro-5-metil-4-((*trans*)-2-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (279)



5-cloro-N2-(2-fluoro-5-metil-4-((*cis*)-2-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (280)



Paso 1: Una solución de 2-metil-4-oxo-piperidin-1-carboxilato de terbutilo (1 gramo, 4.69 milimoles) en tetrahidrofurano (20 mililitros), se agregó por goteo a una solución enfriada (-78°C) y vigorosamente agitada de LDA (3.75 mililitros de una solución 1.5M en ciclohexanos, 5.63 milimoles) en tetrahidrofurano (20 mililitros), bajo N_2. La mezcla de reacción se agitó a -78°C durante 30 minutos antes de agregar una solución de fenil-trifluoro-sulfonimida (1.84 gramos, 5.16 milimoles) en tetrahidrofurano (20 mililitros). En seguida de esta adición, la mezcla de reacción se calentó a temperatura ambiente, y se agitó durante 3 horas. La reacción se enfrió a 0°C, y se apagó con 100 mililitros de NH_4Cl acuoso saturado, seguido por filtración a

través de Celite. El filtrado se agregó a 100 mililitros de EtOAc y las capas se separaron. La capa orgánica se lavó con agua, se secó sobre $MgSO_4$ y se concentró. El producto crudo se purificó mediante cromatografía en gel de sílice (gradiente del 0 al 30 por ciento de EtOAc en hexanos, y se verificó mediante TLC teñida con $KMnO_4$ al 2 por ciento en EtOH), para proporcionar el 2-metil-4-(trifluoro-metil-sulfoniloxi)-5,6-dihidro-piridin-1(2H)-carboxilato de terbutilo como un sólido amarillo.

Paso 2: A una mezcla de 2-fluoro-5-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-anilina (587 miligramos, 2.33 milimoles), 2-metil-4-(trifluoro-metil-sulfoniloxi)-5,6-dihidro-piridin-1(2H)-carboxilato de terbutilo (968 miligramos, 2.80 milimoles), y carbonato de sodio (1.73 gramos, 16.35 milimoles) en N,N-dimetil-formamida / H_2O (20/5 mililitros), se le agregó tetraquis-(trifenil-fosfina)-paladio(0) (135 miligramos, 5 por ciento milimoles). El tubo de reacción se selló, la mezcla se purgó con N_2 durante 3 minutos, y entonces se calentó a 100°C bajo N_2 durante 8 horas. La reacción se enfrió a temperatura ambiente, y se vertió en una solución acuosa saturada de cloruro de amonio. La mezcla de reacción cruda se extrajo con acetato de etilo (15 mililitros, 3 veces). Los extractos orgánicos se combinaron, se lavaron con salmuera, y se concentraron. El producto crudo se purificó mediante cromatografía en gel de sílice (acetato de etilo al 50 por ciento en hexanos), para proporcionar el 4-(4-amino-5-fluoro-2-metil-fenil)-6-metil-5,6-dihidro-piridin-1(2H)-carboxilato de terbutilo como un aceite color amarillo.

El aceite obtenido se disolvió en metanol (20 mililitros). A la solución se le agregó Pd/C (al 10 por ciento). La mezcla de reacción se desgasificó y se purgó con H_2 varias veces, y se agitó vigorosamente bajo 1 atmósfera de H_2 durante la noche. La mezcla se filtró, y el filtrado se concentró, para proporcionar el 4-(4-amino-5-fluoro-2-metil-fenil)-2-metil-piperidin-1-carboxilato de terbutilo como un sólido blanco. ESMS *m/z* 267 (M -56+ H^+).

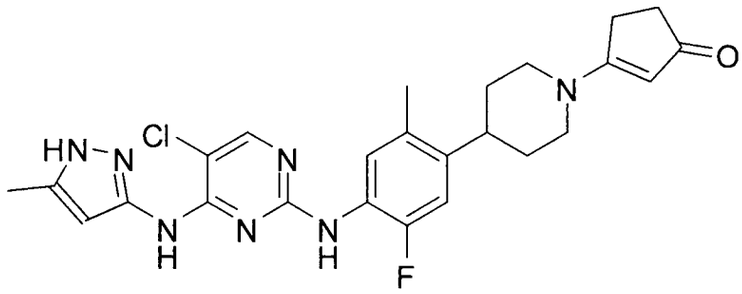
Paso 3: Una mezcla de la 2,5-dicloro-*N*-(5-metil-1H-pirazol-3-il)-pirimidin-4-amina (346 miligramos, 1.42 milimoles), y 4-(4-amino-5-fluoro-2-metil-fenil)-2-metil-piperidin-1-carboxilato de terbutilo (352 miligramos, 1.09 milimoles) en 2-propanol (10 mililitros) se trató con HCl concentrado (12N, 0.43 mililitros). La mezcla se selló y se calentó en un reactor de microondas a 130°C durante 45 minutos. La mezcla se concentró. El residuo se purificó mediante HPLC en fase inversa, para proporcionar la 5-cloro-N2-(2-fluoro-5-metil-4-(2-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un sólido blanco. ESMS *m/z* 430.1 (M + H^+).

Paso 4: La 5-cloro-N2-(2-fluoro-5-metil-4-(2-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (20 miligramos, 0.046 milimoles) se disolvió en una mezcla de solventes de dicloro-metano y metanol (0.5 mililitros, 10/1 por volumen/volumen + NH_3 0.175N). La mezcla se aplicó a cromatografía de capa delgada de preparación con el objeto de separar los estereoisómeros *cis* y *trans* (eluyente: metanol al 6 por ciento en dicloro-metano con NH_3 0.1N) de la 5-cloro-N2-(2-fluoro-5-metil-4-(2-metil-piperidin-4-il)-

fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como sólidos blancos. El isómero *trans* fue la banda superior de la cromatografía de capa delgada de preparación, y el isómero *cis* fue la banda inferior de la cromatografía de capa delgada de preparación; ESMS *m/z* 430.1 ($M + H^+$); estereoisómero *cis*: ^1H RMN (400 MHz, MeOD-d4): δ 8.03 (s, 1H), 7.84 (d, 1H), 7.02 (d, 1H), 6.24 (d, 1H), 3.90-3.85 (m, 1H), 2.32 (s, 3H), 2.27 (s, 3H), 2.03-1.84 (m, 2H), 1.65-1.54 (m, 1H), 1.55 (d, 3H), 1.38-1.19 (m, 4H).

Ejemplo 58

3-(4-(4-(5-cloro-4-(5-metil-1*H*-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-ciclopent-2-en-ona (282)

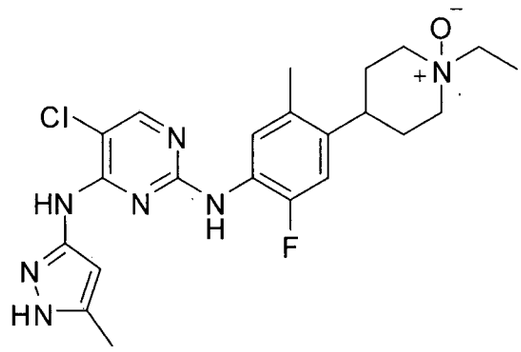


Una mezcla de la 5-cloro-N^2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (43 miligramos, 0.1 milimoles), ciclopentano-1,3-diona (89 miligramos, 9.1 milimoles), ciano-borohidruro de sodio (19 miligramos, 0.3 milimoles), y DIEA (0.2 mililitros, 11 milimoles) en metanol (1 mililitro) se agitó en un frasco sellado a 60°C. Después de 2.5 horas, se agregó ciano-borohidruro de sodio adicional (19 miligramos, 0.3 milimoles), y la reacción se continuó agitándose a 60°C durante la noche. La mezcla se purificó mediante HPLC en fase inversa, para

dar la 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-ciclopent-2-en-ona como un sólido grisáceo; ^{1}H RMN (400 MHz, DMSO-d_6) δ 9.97 (br s, 1H), 9.83 (br s, 1H), 8.90 (s, 1H), 8.32 (d, *J* = 6.8 Hz, 1H), 7.88 (d, *J* = 12.8 Hz, 1H), 6.97 (s, 1H), 6.04 (s, 1H), 5.30 (br s, 1H), 4.71 (d, J = 12.0 Hz, 2H), 4.04 (t, *J* = 12.4 Hz, 2H), 3.84 (m, 1H), 3.53 (m, 2H), 3.13 (m, 2H), 3.08 (s, 3H), 2.96 (s, 3H), 2.59-2.40 (m, 4H); ESMS *m/z* 496.2 (M+H$^+$).

Ejemplo 59

1-óxido de 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-1-etil-piperidina (289)

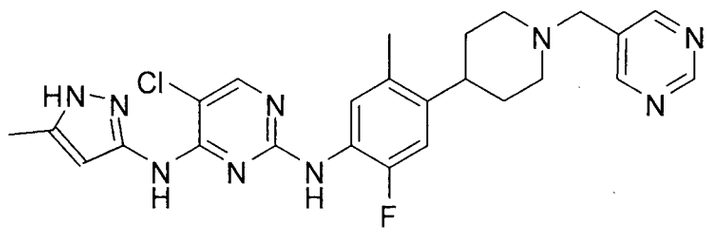


A una solución de la 5-cloro-N^2-(4-(1-etil-piperidin-4-il)-2-fluoro-5-metil-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (22.2 miligramos, 0.05 milimoles) en dicloro-metano (10 mililitros), y metanol (1 mililitro), se le agregó MCPBA (11.2 miligramos, 0.07 milimoles). La reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se dividió entre dicloro-metano y $NaHCO_3$ acuoso saturado, los extractos orgánicos combinados se secaron (Na_2SO_4), y se concentraron al vacío. El producto crudo se

purificó mediante HPLC en fase inversa, para proporcionar el 1-óxido de 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-1-etil-piperidina; ^{1}H RMN (MeOD-d_4) δ7.91 (s, 1H), 7.69 (d, 1H), 7.00 (d, 1H), 6.15 (s, 1H), 3.28 (m, 4H), 2.91 (m, 1H), 2.32 (m, 2H), 2.20 (s, 3H), 2.16 (s, 3H), 1.83 (s, 2H), 1.64 (d, 2H), 1.31 (t, 3H).; ESMS *m/z* 460.2 ($M + H^+$).

Ejemplo 60

5-cloro-N^2-(2-fluoro-5-metil-4-(1-(pirimidin-5-il-metil)-piperidin-4-il)-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina (314)

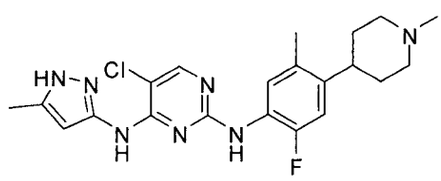


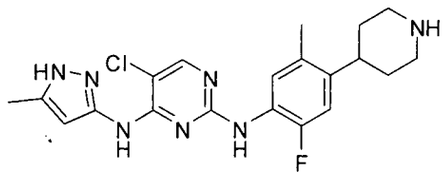
A una solución de la 5-cloro-N^2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina (45 miligramos, 0.1 milimoles), y pirimidin-5-carbaldehído (32 miligramos, 0.3 milimoles) en dicloro-metano (1.5 mililitros), se le agregó $NaBH(OAc)_3$ (64 miligramos, 0.3 milimoles), seguido por la adición de AcOH (12 microlitros). Después de agitar a temperatura ambiente en un frasco sellado durante 16 horas, la reacción se apagó con EtOAc (50 mililitros). La mezcla de reacción se lavó en secuencia con agua (10 mililitros), salmuera (5 mililitros), se secó sobre Na_2SO_4 y se concentró al vacío. El residuo resultante se purificó mediante cromatografía en gel de sílice (del 0 al 10 por ciento de metanol en un gradiente de EtOAc con un aditivo de NH_3 al 1 por ciento en

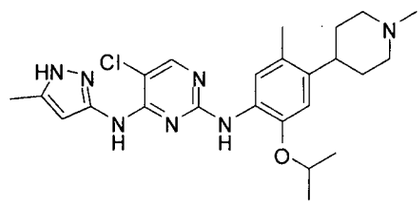
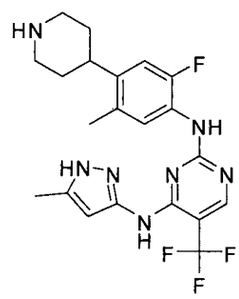
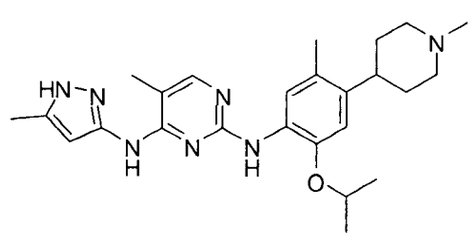
metanol), para dar la 5-cloro-N2-(2-fluoro-5-metil-4-(1-(pirimidin-5-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina como un sólido grisáceo; ^{1}H RMN (400 MHz, CD_3OD) δ 9.09 (s, 1H), 8.81 (s, 2H), 8.00 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 13.2 Hz, 1H), 6.23 (br s, 1H), 3.65 (s, 2H), 3.03 (m, 2H), 2.76 (m, 1H), 2.27 (s, 3H), 2.25 (s, 3H), 2.25 (m, 2H), 1.80-1.68 (m, 4H); ESMS *m/z* 508.2 ($M+H^+$).

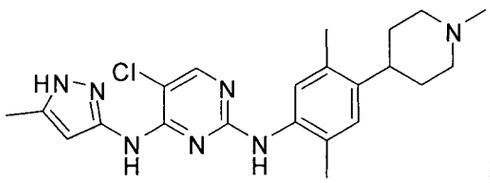
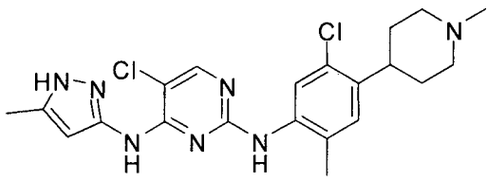
Los siguientes compuestos en la Tabla 1 se obtienen repitiendo los procedimientos descritos en los Ejemplos anteriores, y utilizando los materiales de partida apropiados.

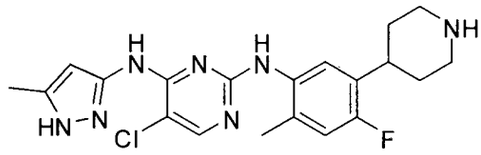
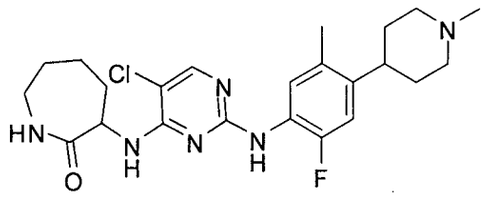
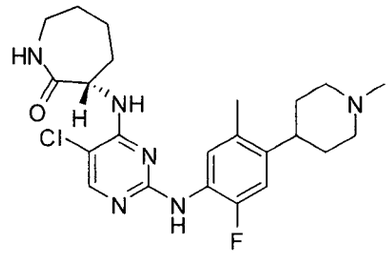
Tabla 1

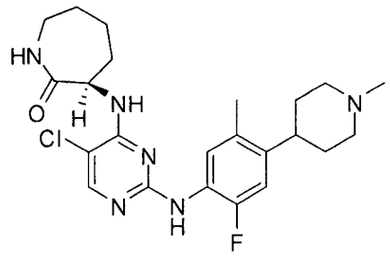
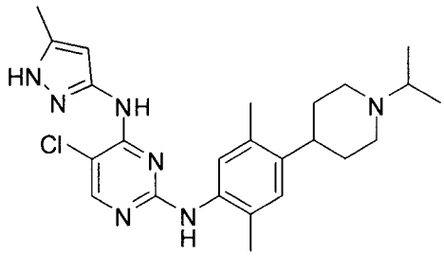
	ESTRUCTURA	**RMN o ESMS**	**IGF-1R Ba/F3 IC_{50} (μM)**
X	 5-cloro-N2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	^{1}H RMN (400 MHz, DMSO-d6) δ 10.33 (br, 1H), 9.90 (br, 1H0, 9.60 (br, 1H), 8.22 (s, 1H), 7.56 (d, 1H), 7.00 (d, 1H), 6.20 (s, 1H), 3.53-3.50	0.011

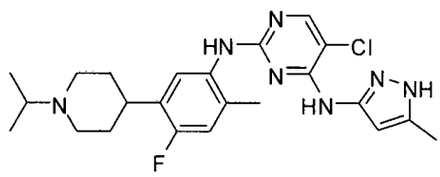
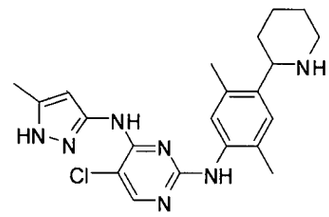
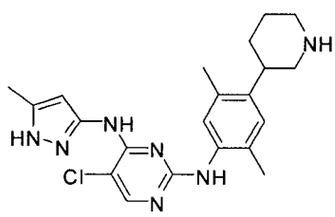
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
		(m, 2H), 3.16-3.10 (m, 2H), 2.97-2.92 (m,1H), 2.81 (d, 3H), 2.26 (s, 3H), 2.16 (s, 3H), 1.94-1.91 (m, 2H), 1.83-1.73 (m, 2H); ESMS *m/z* 430.1 ($M + H^+$).	
X	 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 416.1 ($M + H^+$).	0.050

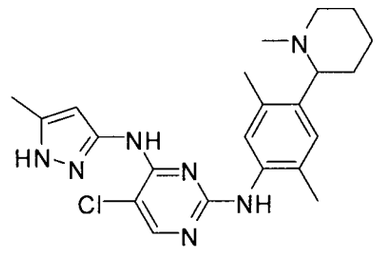
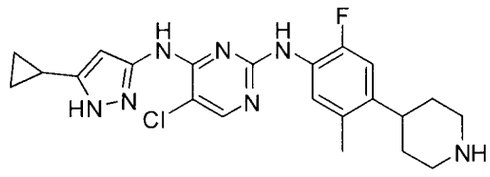
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
X	 5-cloro-N2-(2-isopropoxi-5-metil-4-(1-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 470.2 ($M + H^+$).	0.104
	 N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-5-(trifluoro-metil)-pirimidin-2,4-diamina	ESMS *m/z* 450.2 ($M + H^+$).	0.150
X		ESMS *m/z* 450.3 ($M + H^+$).	0.805

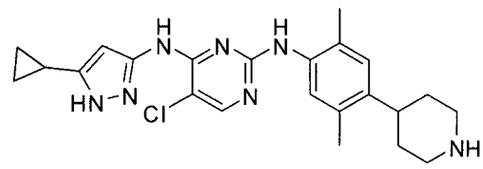
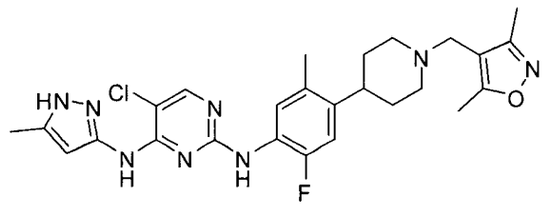
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	N2-(2-isopropoxi-5-metil-4-(1-metil-piperidin-4-il)-fenil)-5-metil-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina		
X	 5-cloro-N2-(2,5-dimetil-4-(1-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 426.2 ($M + H^+$).	0.015
X	 5-cloro-N2-(5-cloro-2-metil-4-(1-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 446.1 ($M + H^+$).	0.015
		ESMS *m/z* 461.2 ($M + H^+$).	1.93

	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(4-fluoro-2-metil-5-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina		
X	 3-(5-cloro-2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil-amino)-pirimidin-4-il-amino)-azepan-2-ona	ESMS *m/z* 461.2 ($M + H^+$).	0.087
	 (S)-3-(5-cloro-2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil-amino)-pirimidin-4-il-amino)-	ESMS *m/z* 461.2 ($M + H^+$).	0.869

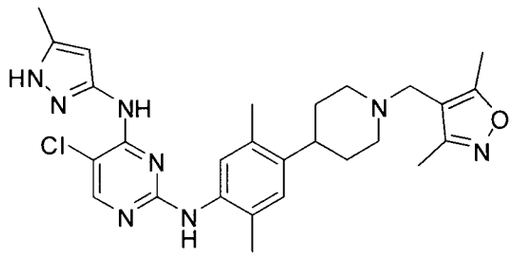
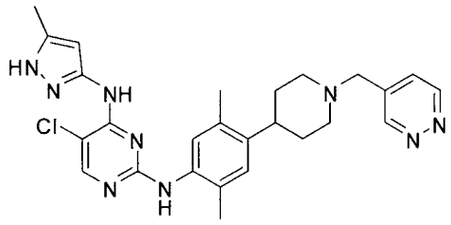
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	azepan-2-ona		
	 (R)-3-(5-cloro-2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil-amino)-pirimidin-4-il-amino)-azepan-2-ona	ESMS *m/z* 461.2 ($M + H^+$).	0.065
	 5-cloro-N2-(4-(1-isopropil-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 454.2 ($M + H^+$).	0.010

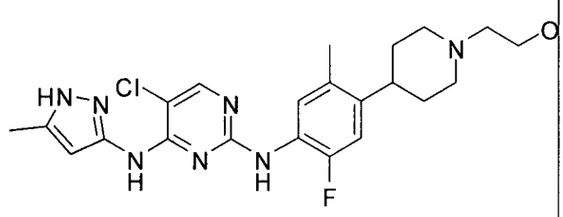
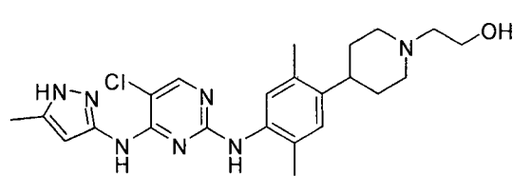
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(4-fluoro-5-(1-isopropil-piperidin-4-il)-2-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 458.2 ($M + H^+$).	
	 5-cloro-N2-(2,5-dimetil-4-(piperidin-2-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS m/z 412.2 (M + H+).	0.016
	 5-cloro-N2-(2,5-dimetil-4-(piperidin-3-il)-fenil)-N4-(5-metil-	ESMS *m/z* 412.2 ($M + H^+$).	0.050

	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	1H-pirazol-3-il)-pirimidin-2,4-diamina		
	 5-cloro-N2-(2,5-dimetil-4-(1-metil-piperidin-2-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 426.2 ($M + H^+$).	0.019
	 5-cloro-N4-(5-ciclopropil-1H-pirazol-3-il)-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-pirimidin-2,4-diamina	ESMS *m/z* 442.2 ($M + H^+$).	0.160

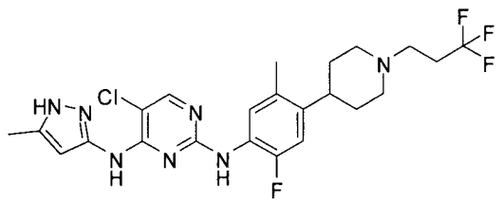
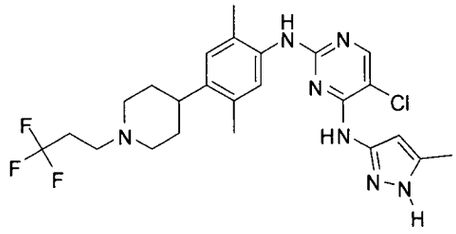
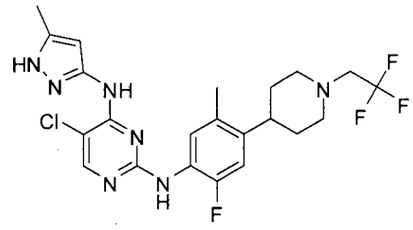
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N4-(5-ciclopropil-1H-pirazol-3-il)-N2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-pirimidin-2,4-diamina	ESMS *m/z* 438.2 ($M + H^+$).	0.095
	 5-cloro-N2-(4-(1-((3,5-dimetil-isoxazol-4-il)-metil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	^{1}H RMN (400 MHz, MeOD-d4) 8.12 (s, 1H), 7.75 (d, 1H), 7.03 (s, 1H), 6.27 (s, 1H), 4.25 (s, 2H), 3.69-3.67 (m, 2H), 3.27-3.20 (m, 3H), 2.54 (s, 3H), 2.37 (s, 3H), 2.34 (s,	0.056

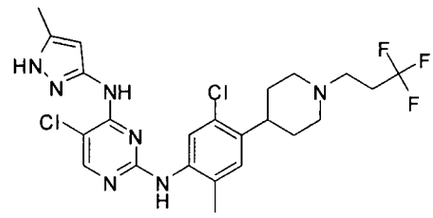
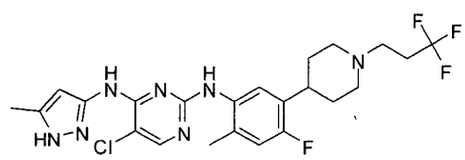
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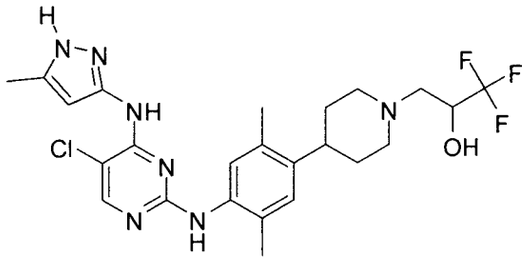
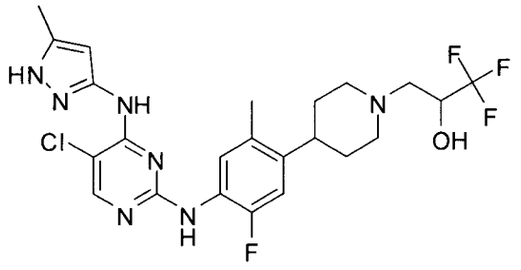
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
		3H), 2.30 (s, 3H), 2.10-1.95 (m, 4H);ESMS m/z 525.1 (M + H+).	
	 5-cloro-N2-(4-(1-((3,5-dimetil-isoxazol-4-il)-metil)-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 521.2 ($M + H^+$).	0.011
	 5-cloro-N2-(2,5-dimetil-4-(1-(piridazin-4-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-	ESMS *m/z* 504.2 ($M + H^+$)	0.002

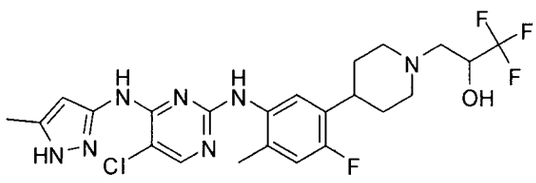
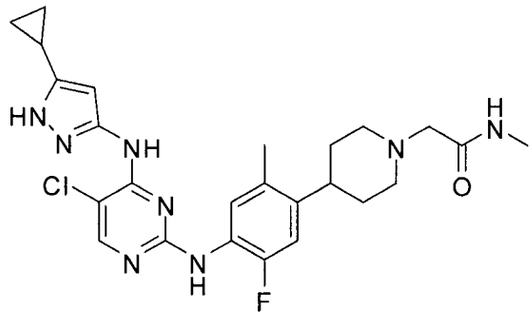
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	il)-pirimidin-2,4-diamina		
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-etanol	ESMS m/z 460.2 (M + H+).	0.059
X	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-etanol	ESMS *m/z* 456.21 (M + H^+).	0.006

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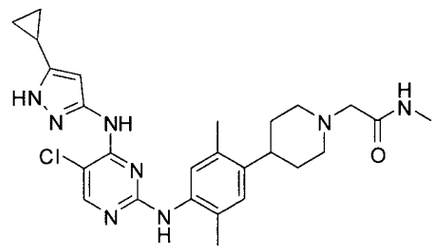
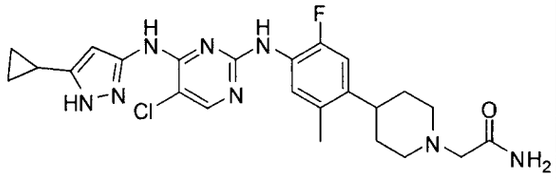
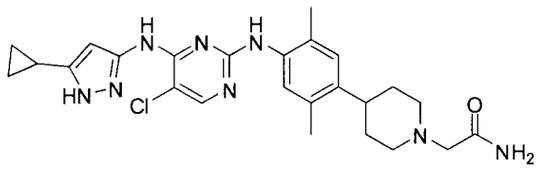
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N^2-(2-fluoro-5-metil-4-(1-(3,3,3-trifluoro-propil)-piperidin-4-il)-fenil)- N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 512.2 ($M + H^+$).	0.085
	 5-cloro-N2-(2,5-dimetil-4-(1-(3,3,3-trifluoro-propil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 508.2 ($M + H^+$).	0.031
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-	ESMS *m/z* 498.2 ($M + H^+$).	0.142

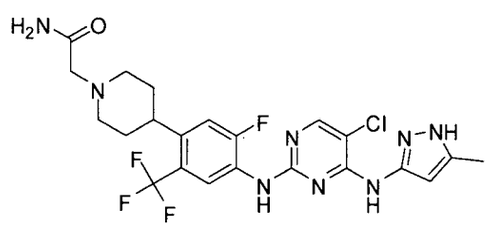
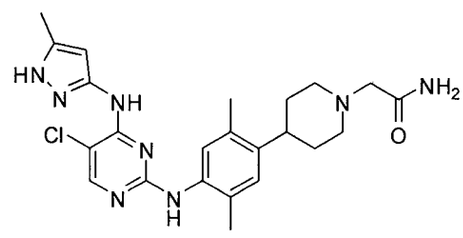
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	(2,2,2-trifluoro-etil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina		
	 5-cloro-N2-(5-cloro-2-metil-4-(1-(3,3,3-trifluoro-propil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 528.2 ($M + H^+$).	0.044
	 5-cloro-N2-(4-fluoro-2-metil-5-(1-(3,3,3-trifluoro-propil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 512.2 ($M + H^+$).	5.46

	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol	ESMS *m/z* 524.2 ($M + H^+$).	0.023
	 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino) pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol	ESMS *m/z* 528.2 ($M + H^+$).	0.071

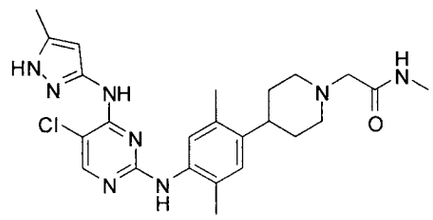
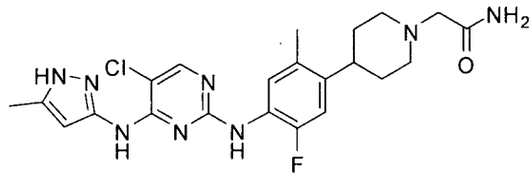
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 3-(4-(5-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2-fluoro-4-metil-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol	ESMS m/z 528.2 (M + H+).	6.47
	 2-(4-(4-(5-cloro-4-(5-ciclopropil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-N-metil-acetamida	ESMS *m/z* 513.2 ($M + H^+$).	0.042

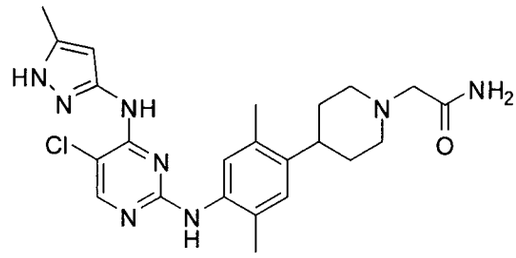
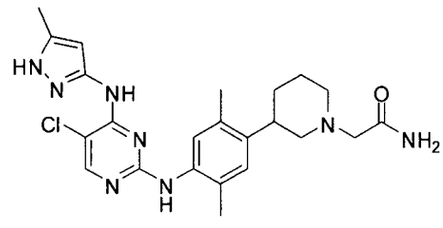
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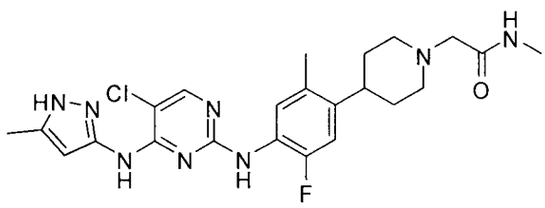
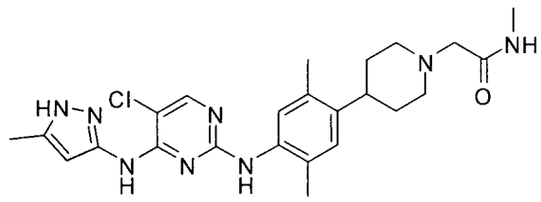
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 2-(4-(4-(5-cloro-4-(5-ciclopropil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida	ESMS *m/z* 509.2 ($M + H^+$).	0.006
	 2-(4-(4-(5-cloro-4-(5-ciclopropil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-acetamida	ESMS *m/z* 499.2 ($M + H^+$).	0.049
	 2-(4-(4-(5-cloro-4-(5-ciclopropil-	ESMS *m/z* 495.2 ($M + H^+$).	0.011

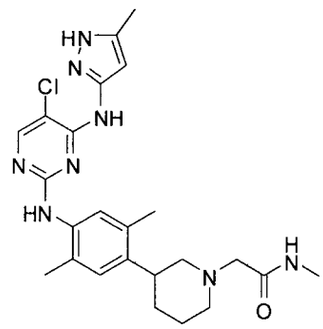
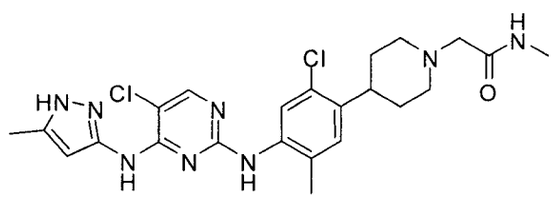
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-acetamida		
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-(trifluoro-metil)-fenil)-piperidin-1-il)-acetamida	ESMS *m/z* 527.2 ($M + H^+$).	0.019
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-acetamida	ESMS *m/z* 469.2 ($M + H^+$).	0.013

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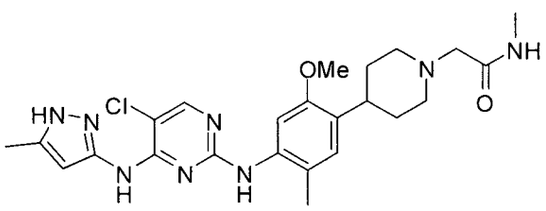
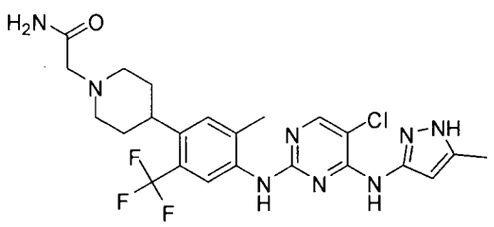
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida	ESMS *m/z* 483.2 ($M + H^+$).	0.010
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-acetamida	^{1}H RMN (400 MHz, MeOD-d_4) δ 8.11 (s, 1H), 7.76 (d 1H), 7.09 (d, 1H), 6.27 (s, 1H), 4.0 (s, 2H), 3.75-3.73 (m, 2H), 3.22-3.13 (m, 3H), 2.34 (s, 3H), 2.30 (s, 3H), 2.04 -2.00 (m, 4H); ESMS	0.019

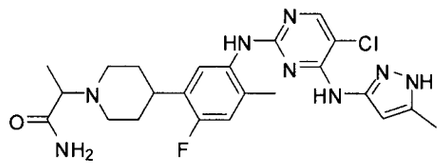
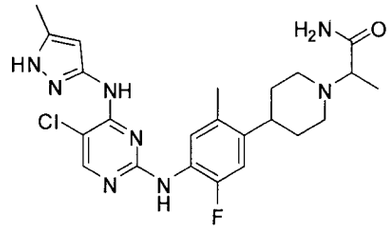
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
		m/z 473.2 (M + H^+).	
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-acetamida	ESMS *m/z* 469.2 (M + H^+).	
	 2-(3-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-acetamida	ESMS *m/z* 469.2 (M + H^+).	0.026

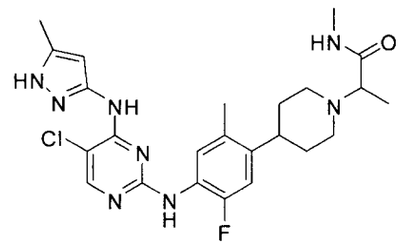
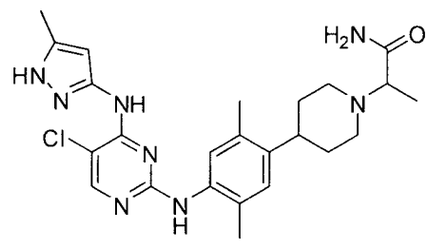
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
X	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-N-metil-acetamida	ESMS *m/z* 487.2 ($M + H^+$).	0.019
X	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida	ESMS *m/z* 483.2 ($M + H^+$).	

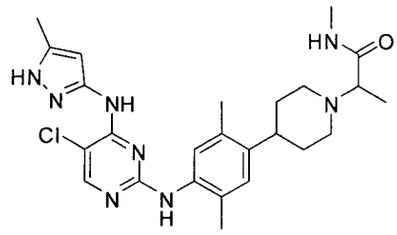
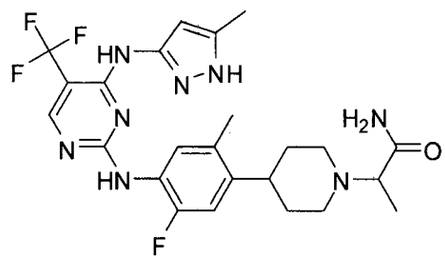
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 2-(3-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida	ESMS *m/z* 483.2 ($M + H^+$).	0.015
X	 2-(4-(2-cloro-4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-metil-fenil)-piperidin-1-il)-N-metil-acetamida	ESMS *m/z* 503.2 ($M + H^+$).	0.018

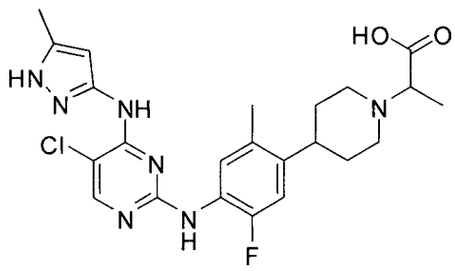
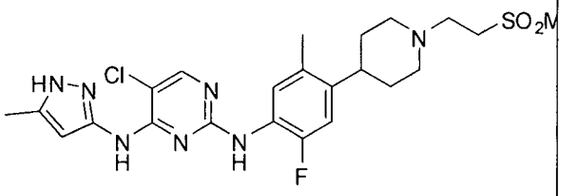
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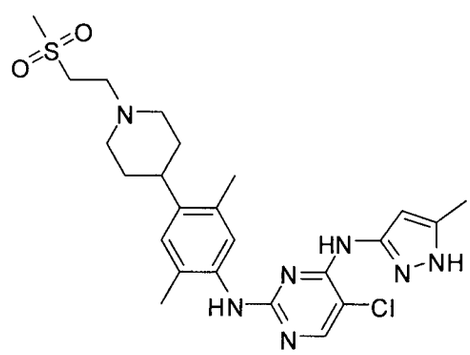
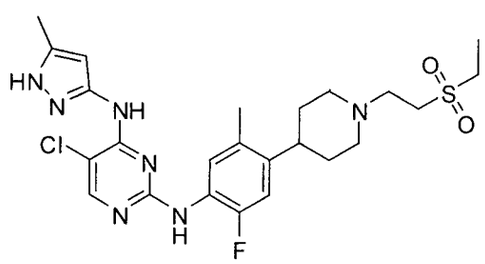
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
X	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2-metoxi-5-metil-fenil)-piperidin-1-il)-N-metil-acetamida	ESMS *m/z* 499.2 ($M + H^+$).	0.013
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-metil-2-(trifluoro-metil)-fenil)-piperidin-1-il)-acetamida	ESMS *m/z* 523.2 ($M + H^+$).	0.022

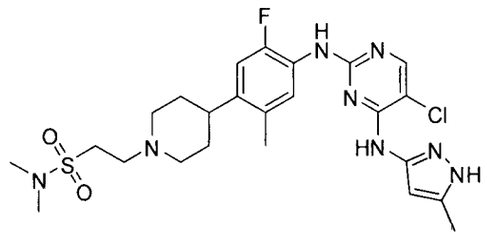
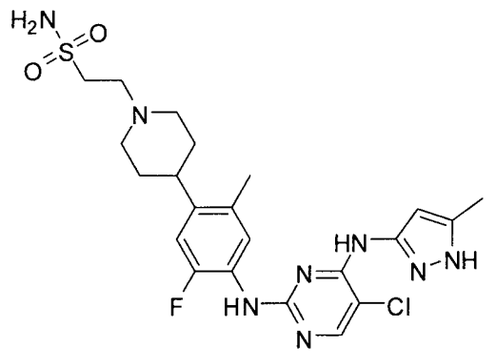
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 2-(4-(5-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2-fluoro-4-metil-fenil)-piperidin-1-il)-propanamida	ESMS *m/z* 487.2 ($M + H^+$).	3.68
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propanamida	ESMS *m/z* 487.2 ($M + H^+$).	0.015

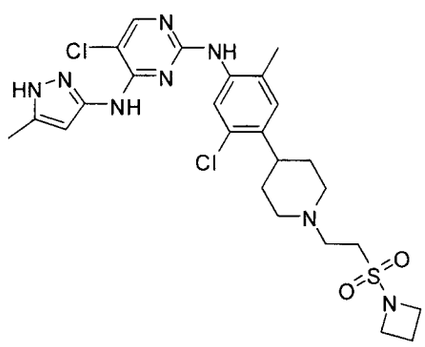
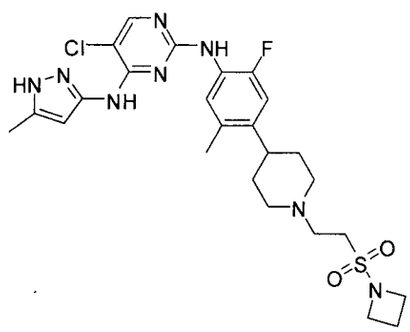
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-N-metil-propanamida	ESMS m/z 501.2 (M + H+).	0.022
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-propanamida	ESMS *m/z* 483.2 (M + H^+).	0.009

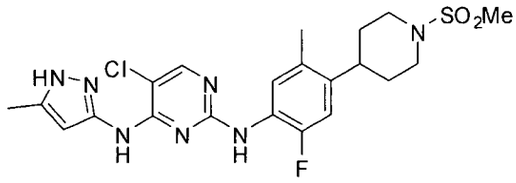
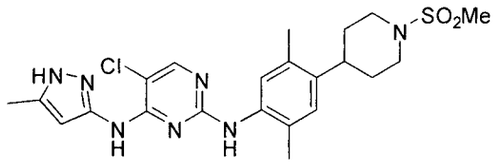
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-propanamida	ESMS *m/z* 497.2 ($M + H^+$).	0.006
	 2-(4-(5-fluoro-2-metil-4-(4-(5-metil-1H-pirazol-3-il-amino)-5-(trifluoro-metil)-pirimidin-2-il-amino)-fenil)-piperidin-1-il)-propanamida	ESMS *m/z* 521.2 ($M + H^+$).	0.078

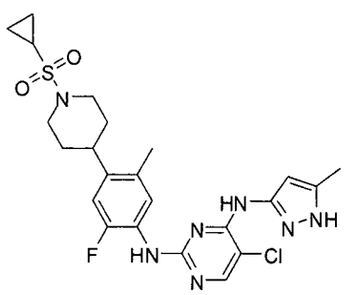
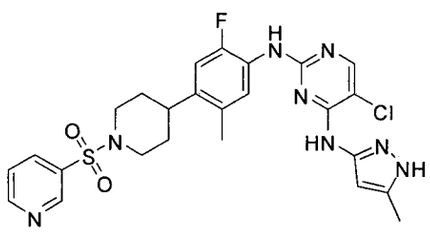
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 ácido 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propanoico	ESMS *m/z* 488.2 ($M + H^+$).	1.53
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(2-(metil-sulfonil)-etil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS m/z 522.1 (M + H+).	0.024

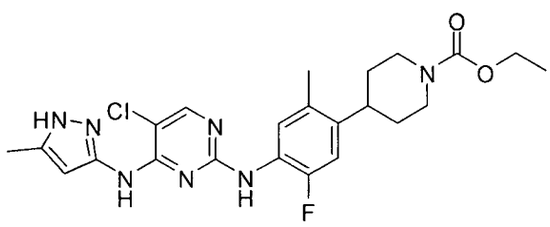
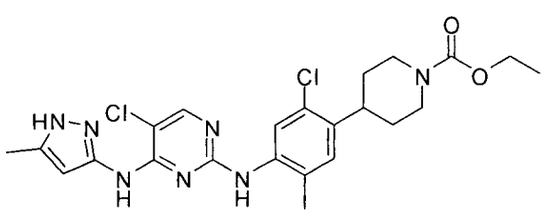
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(2,5-dimetil-4-(1-(2-(metil-sulfonil)-etil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 518.2 ($M + H^+$).	0.006
	 5-cloro-N2-(4-(1-(2-(etil-sulfonil)-etil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 536.2 ($M + H^+$).	0.021

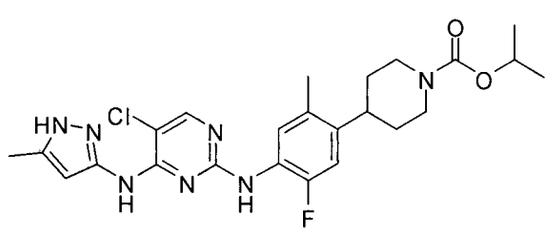
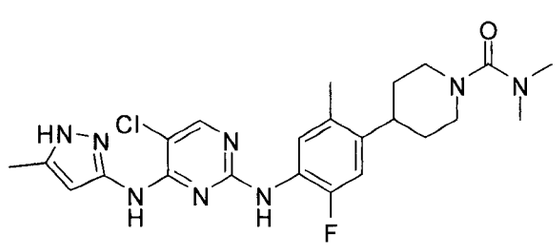
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-N,N-dimetil-etan-sulfonamida	ESMS *m/z* 551.2 ($M + H^+$).	0.036
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-etan-sulfonamida	ESMS *m/z* 523.2 ($M + H^+$).	0.038

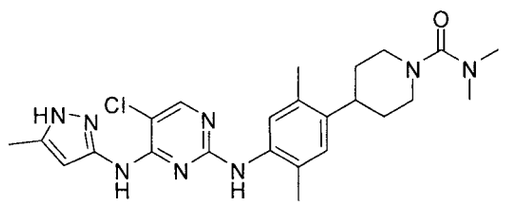
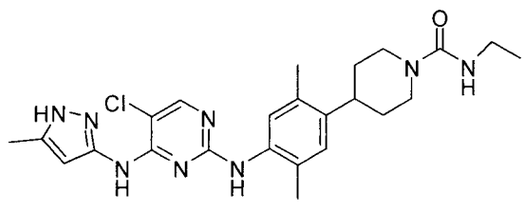
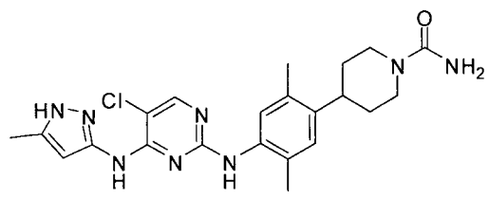
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 N2-(4-(1-(2-(azetidin-1-il-sulfonil)-etil)-piperidin-4-il)-5-cloro-2-metil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 579.2 ($M + H^+$).	0.011
	 N2-(4-(1-(2-(azetidin-1-il-sulfonil)-etil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 563.2 ($M + H^+$).	0.056

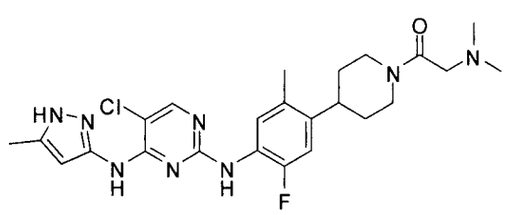
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(metil-sulfonil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 494.2 ($M + H^+$).	0.005
X	 5-cloro-N2-(2,5-dimetil-4-(1-(metil-sulfonil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 490.2 ($M + H^+$).	0.002

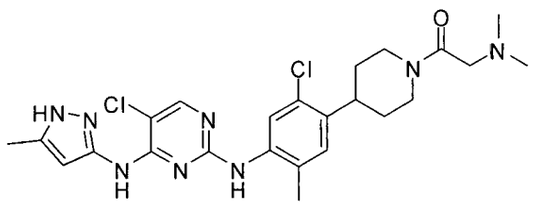
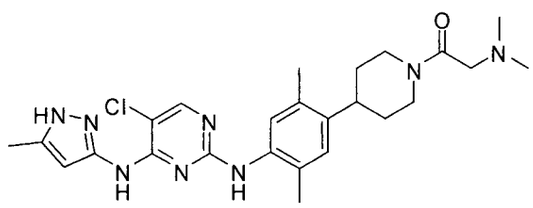
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(4-(1-(ciclopropil-sulfonil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 520.2 ($M + H^+$).	0.059
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(piridin-3-il-sulfonil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 557.2 ($M + H^+$).	0.076

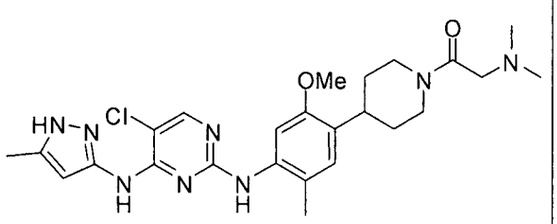
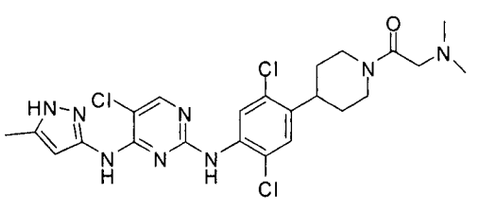
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-carboxilato de etilo	^{1}H RMN (400 MHz, MeOD-d_4) δ 8.13 (s, 1H), 7.54 (d, 1H), 7.10 (d, 1H), 6.28 (s, 1H), 4.30-4.26 (m, 2H), 4.14 (q, 2H), 2.99-2.96 (m, 3H), 2.33 (s, 3H), 2.29 (s, 3H), 1.8-1.77 (m, 2H), 1.64-1.55 (m, 2H), 1.28 (t, 3H); ESMS *m/z* 488.2 (M + H^+).	0.064
X		ESMS *m/z* 504.2 (M + H^+).	0.182

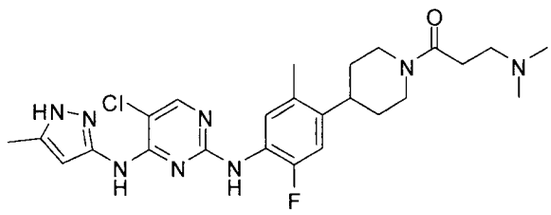
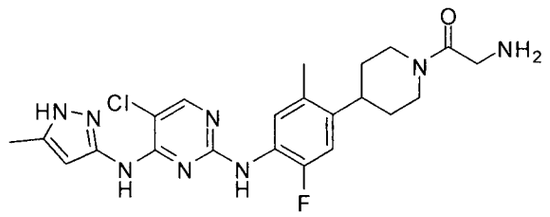
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	4-(2-cloro-4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-metil-fenil)-piperidin-1-carboxilato de etilo		
X	 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-carboxilato de isopropilo	ESMS *m/z* 502.2 ($M + H^+$).	0.080
	 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-N,N-	ESMS m/z 487.2 (M + H+).	0.011

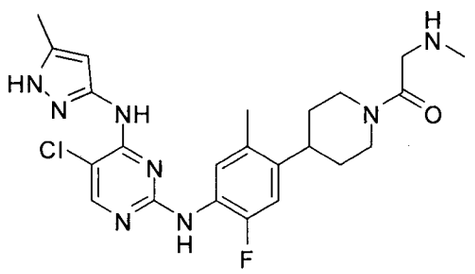
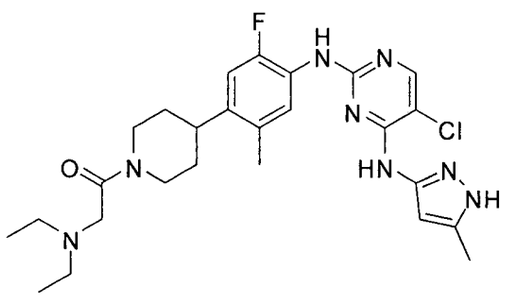
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	dimetil-piperidin-1-carboxamida		
X	 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-N,N-dimetil-piperidin-1-carboxamida	ESMS *m/z* 483.2 ($M + H^+$).	0.006
X	 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-N-etil-piperidin-1-carboxamida	ESMS *m/z* 483.2 ($M + H^+$).	0.002
X		ESMS *m/z* 455.2 ($M + H^+$).	0.006

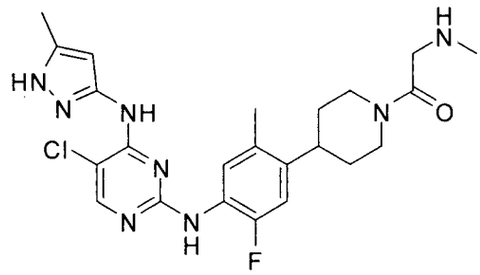
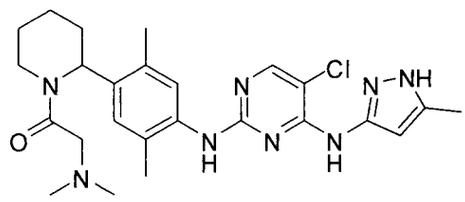
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-carboxamida		
X	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona	^{1}H RMN (400 MHz, MeOD-d_4) δ 8.08 (s, 1H), 7.71 (d, 1H), 7.03 (d, 1H), 6.26 (s, 1H), 4.71-4.67 (m, 2H), 3.81-3.77 (m, 2H), 3.14-3.12 (m, 2H), 2.98 (s, 3H), 2.96 (s, 3H), 2.90-2.83 (m, 1H), 2.34 (s, 3H), 2.28 (s, 3H), 1.87 (d, 2H), 1.76-1.55	0.019

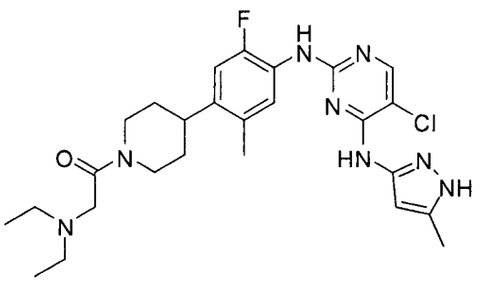
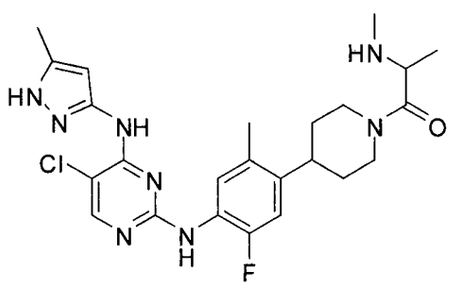
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
		(m, 2H); ESMS *m/z* 501.2 (M + H^+).	
X	 1-(4-(2-cloro-4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-metil-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona	ESMS *m/z* 517.2 (M + H^+).	0.007
X	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona	ESMS *m/z* 497.2 (M + H^+).	0.011

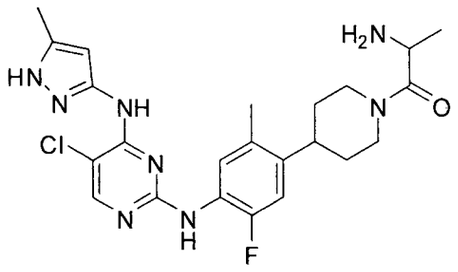
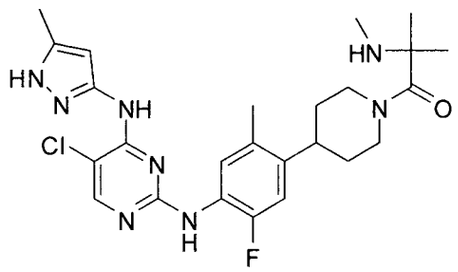
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
X	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2-metoxi-5-metil-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona	ESMS *m/z* 513.2 ($M + H^+$).	0.009
X	 1-(4-(2,5-dicloro-4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona	ESMS *m/z* 537.1 ($M + H^+$).	0.007

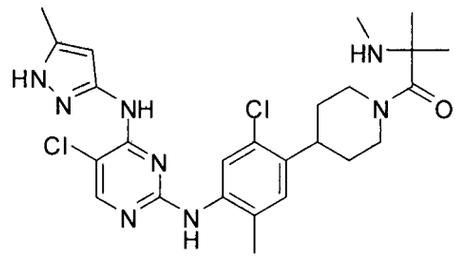
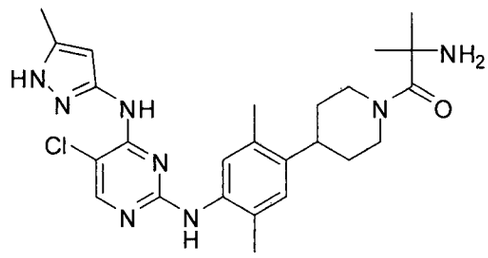
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
X	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-3-(dimetil-amino)-propan-1-ona	ESMS *m/z* 515.2 ($M + H^+$).	0.138
X	 2-amino-1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-etanona	ESMS *m/z* 473.2 ($M + H^+$).	0.075

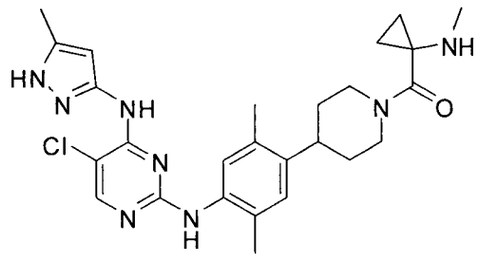
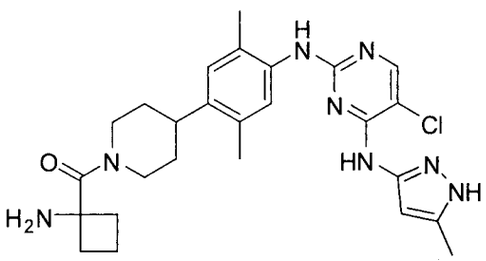
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(metil-amino)-etanona	ESMS *m/z* 487.2 ($M + H^+$).	0.103
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(dietil-amino)-etanona	ESMS *m/z* 529.3 ($M + H^+$).	0.030

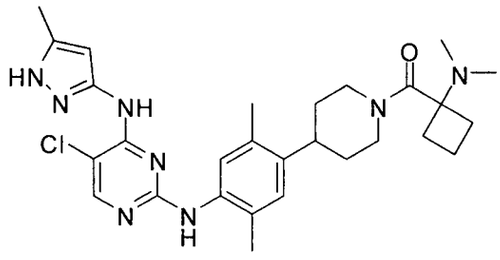
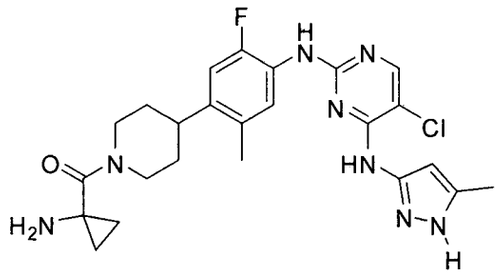
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(metil-amino)-etanona	ESMS *m/z* 487.2 ($M + H^+$).	
	 1-(2-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona	ESMS *m/z* 497.2 ($M + H^+$).	0.013

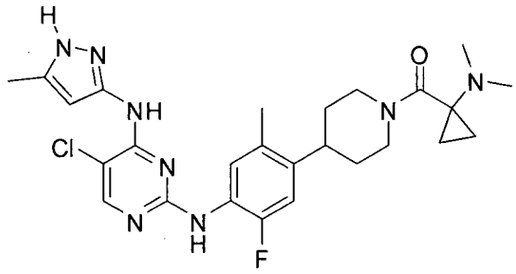
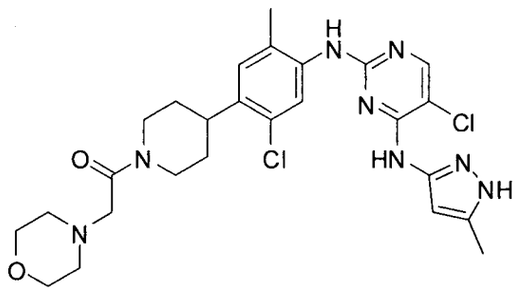
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(dietil-amino)-etanona	ESMS *m/z* 529.3 ($M + H^+$).	
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(metil-amino)-propan-1-ona	ESMS *m/z* 501.2 ($M + H^+$).	0.042

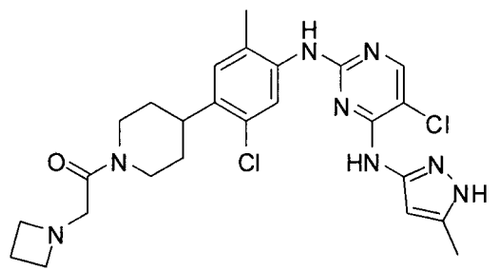
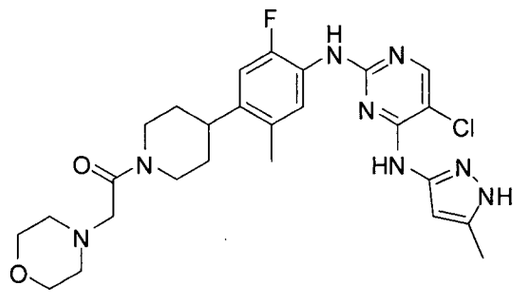
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 2-amino-1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propan-1-ona	ESMS *m/z* 487.2 ($M + H^+$).	0.141
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-metil-2-(metil-amino)-propan-1-ona	ESMS *m/z* 515.2 ($M + H^+$).	0.017

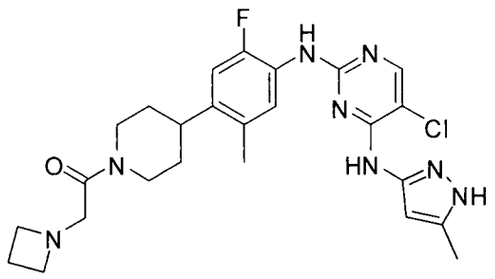
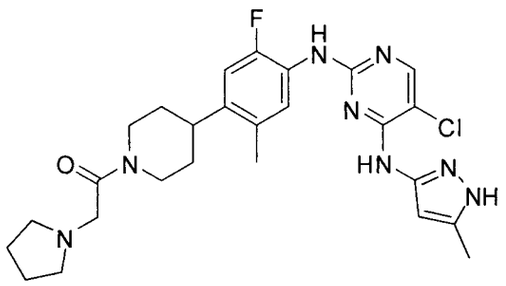
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 1-(4-(2-cloro-4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-metil-fenil)-piperidin-1-il)-2-metil-2-(metil-amino)-propan-1-ona	ESMS *m/z* 531.2 ($M + H^+$).	0.007
	 2-amino-1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-metil-propan-1-ona	ESMS *m/z* 497.2 ($M + H^+$).	0.023

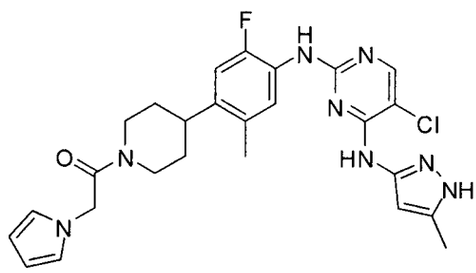
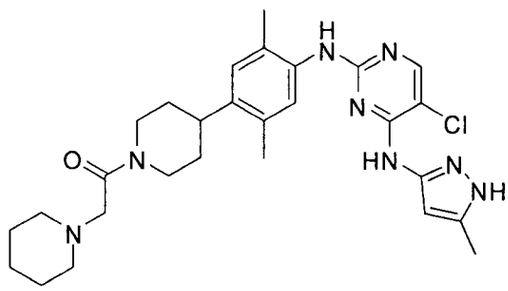
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(1-(metil-amino)-ciclopropil)-metanona	ESMS *m/z* 509.2 ($M + H^+$).	0.005
	 (1-amino-ciclobutil)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-metanona	ESMS *m/z* 509.2 ($M + H^+$).	0.052

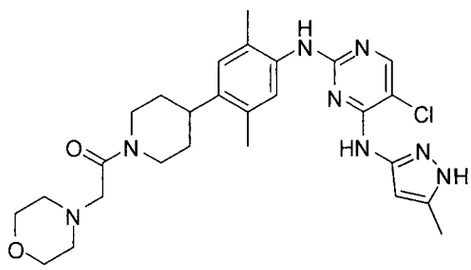
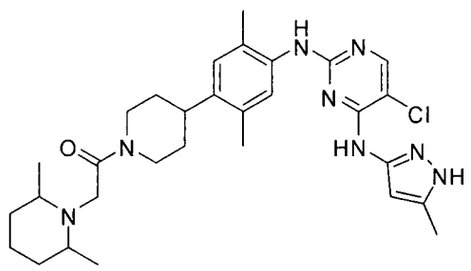
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(1-(dimetil-amino)-ciclobutil)-metanona	ESMS *m/z* 537.3 ($M + H^+$).	0.015
	 (1-amino-ciclopropil)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-metanona	ESMS *m/z* 499.2 ($M + H^+$).	0.033

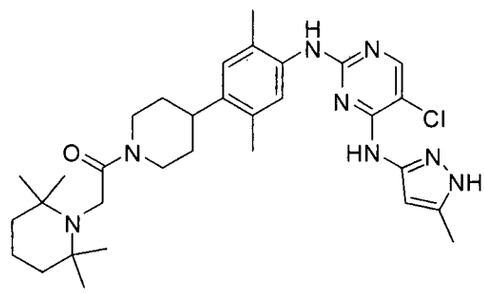
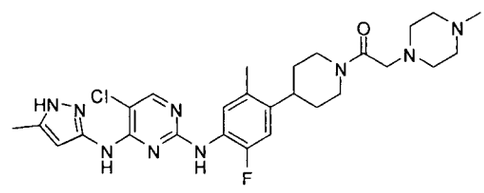
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-(dimetil-amino)-ciclopropil)-metanona	ESMS *m/z* 527.2 ($M + H^+$).	0.013
	 1-(4-(2-cloro-4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-metil-fenil)-piperidin-1-il)-2-morfolino-etanona	ESMS *m/z* 559.2 ($M + H^+$).	0.006

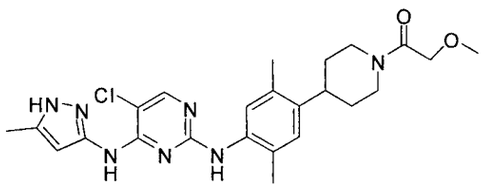
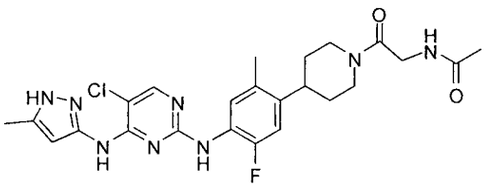
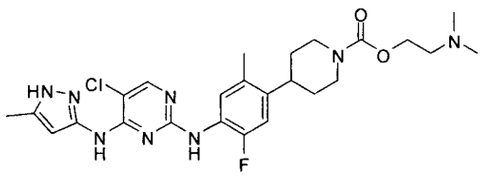
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 2-(azetidin-1-il)-1-(4-(2-cloro-4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-metil-fenil)-piperidin-1-il)-etanona	ESMS *m/z* 529.2 ($M + H^+$).	0.024
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-morfolino-etanona	ESMS *m/z* 543.2 ($M + H^+$).	0.020

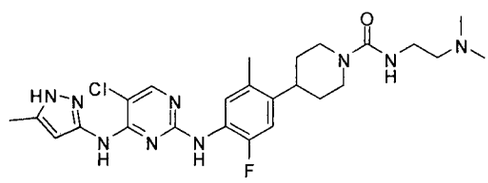
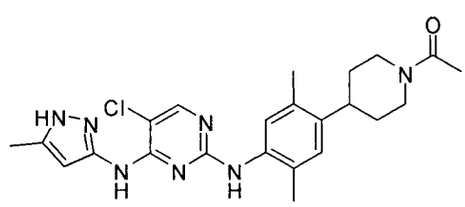
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 2-(azetidin-1-il)-1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-etanona	ESMS *m/z* 513.2 ($M + H^+$).	0.064
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(pirrolidin-1-il)-etanona	ESMS *m/z* 527.2 ($M + H^+$).	0.038

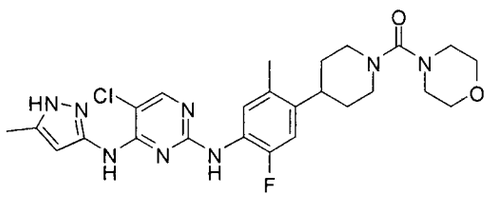
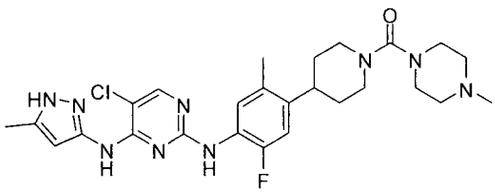
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(1H-pirrol-1-il)-etanona	ESMS *m/z* 523.2 ($M + H^+$).	0.025
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(piperidin-1-il)-etanona	ESMS *m/z* 537.3 ($M + H^+$).	0.007

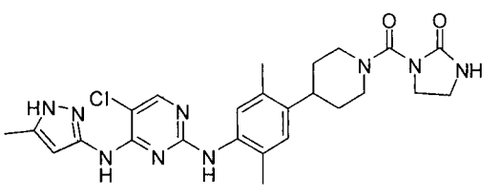
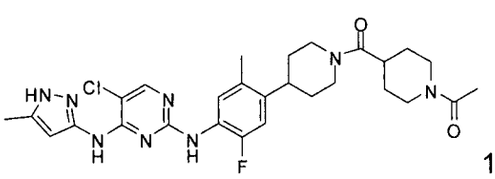
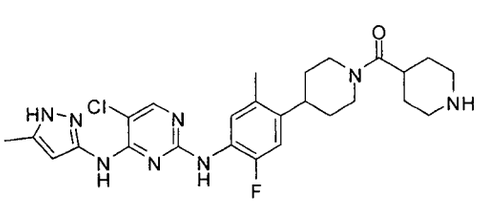
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-morfolino-etanona	ESMS *m/z* 539.3 ($M + H^+$).	0.009
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(2,6-dimetil-piperidin-1-il)-etanona	ESMS *m/z* 565.3 ($M + H^+$).	0.009

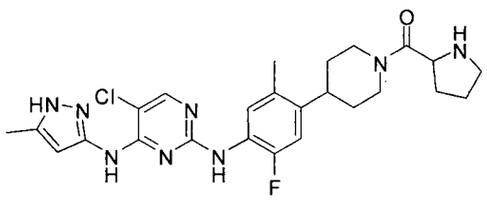
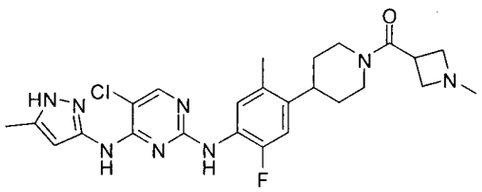
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(2,2,6,6-tetrametil-piperidin-1-il)-etanona	ESMS *m/z* 593.3 ($M + H^+$).	0.018
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(4-metil-piperazin-1-il)-etanona	ESMS m/z 556.3 ($M + H^+$).	0.051

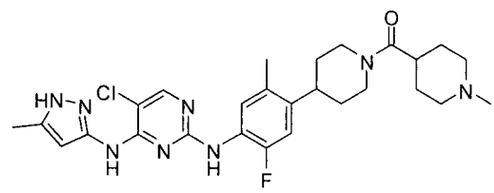
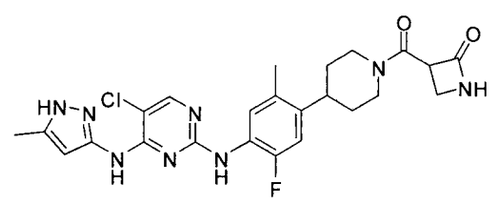
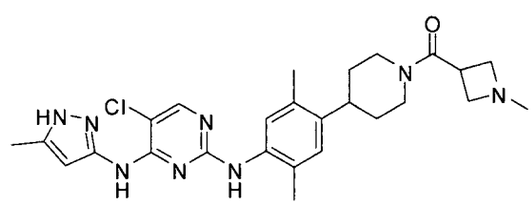
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
X	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-metoxi-etanona	ESMS *m/z* 484.2 ($M + H^+$).	0.002
X	 N-(2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-oxoetil)-acetamida	ESMS *m/z* 515.2 ($M + H^+$).	0.057
X	 2-(dimetil-amino)-4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-	ESMS *m/z* 531.2 ($M + H^+$).	0.053

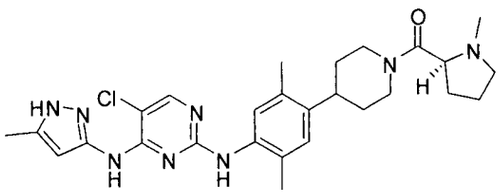
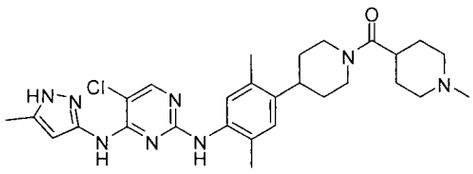
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	metil-fenil)-piperidin-1-carboxilato de etilo		
X	 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-N-(2-(dimetil-amino)-etil)-piperidin-1-carboxamida	ESMS *m/z* 530.2 ($M + H^+$).	0.060
X	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-etanona	ESMS *m/z* 454.2 ($M + H^+$).	0.013

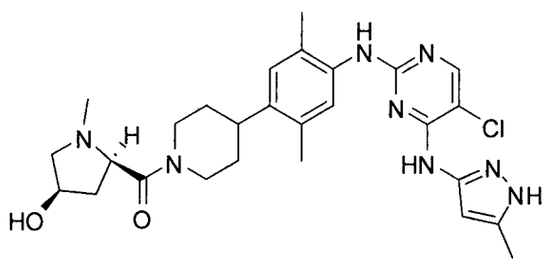
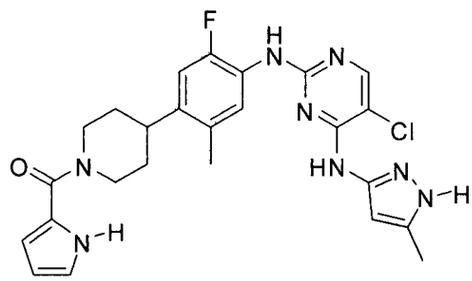
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
X	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(morfolino)-metanona	ESMS *m/z* 529.2 ($M + H^+$).	0.008
X	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(4-metil-piperazin-1-il)-metanona	ESMS *m/z* 542.2 ($M + H^+$).	0.021

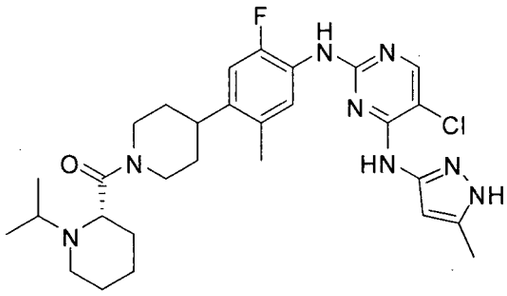
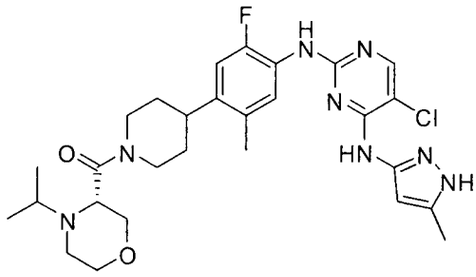
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
X	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-carbonil)-imidazolidin-2-ona	ESMS *m/z* 524.2 ($M + H^+$).	0.013
X	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-metoxi-etanona	ESMS *m/z* 569.2 ($M + H^+$).	0.048
X	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-	ESMS *m/z* 527.2 ($M + H^+$).	1.57

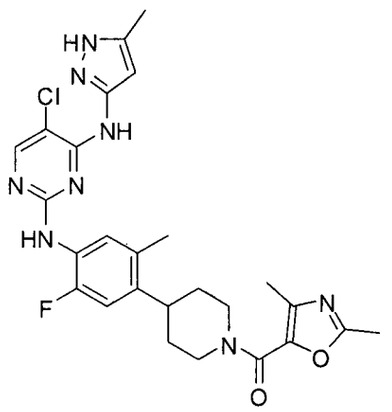
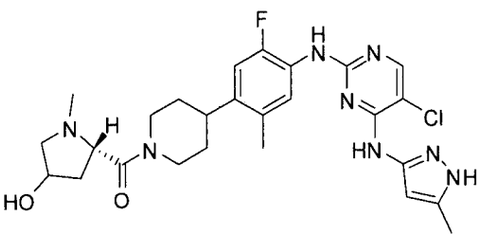
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	piperidin-1-il)-(piperidin-4-il)-metanona		
X	 (S)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(pirrolidin-2-il)-metanona	ESMS *m/z* 513.2 ($M + H^+$).	0.137
X	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-metilazetidin-3-il)-metanona	ESMS *m/z* 513.2($M + H^+$).	0.099

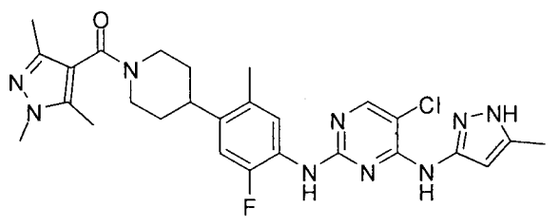
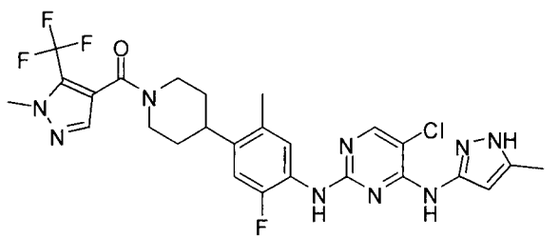
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
X	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-metil-piperidin-4-il)-metanona	ESMS *m/z* 541.2 ($M + H^+$).	0.081
X	 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-carbonil)-azetidin-2-ona	ESMS *m/z* 513.2 ($M + H^+$).	2.99
X		ESMS *m/z* 509.2 ($M + H^+$).	0.025

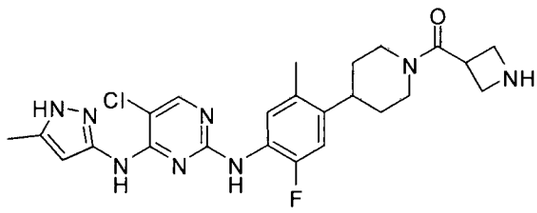
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(1-metilazetidin-3-il)-metanona		
X	 (*S*)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(1-metil-pirrolidin-2-il)-metanona	ESMS *m/z* 523.2 ($M + H^+$).	0.017
X	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(1-metil-piperidin-4-il)-	ESMS *m/z* 537.2 ($M + H^+$).	

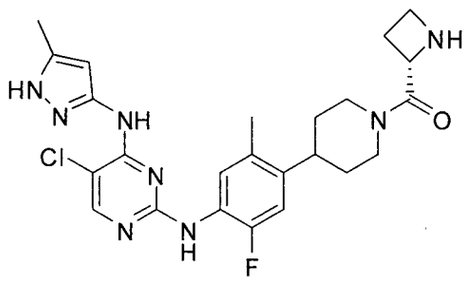
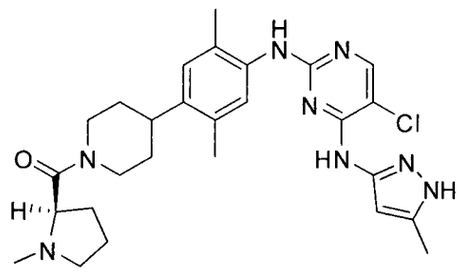
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	metanona		
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-((2R,4R)-4-hidroxi-1-metil-pirrolidin-2-il)-metanona	ESMS *m/z* 539.3 ($M + H^+$).	0.048
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1H-pirrol-2-il)-metanona	ESMS *m/z* 509.2 ($M + H^+$).	0.145

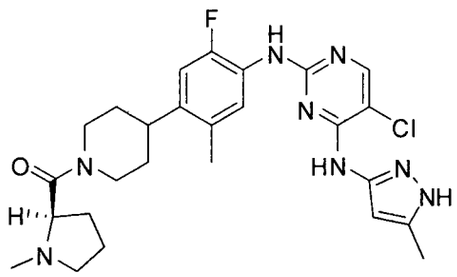
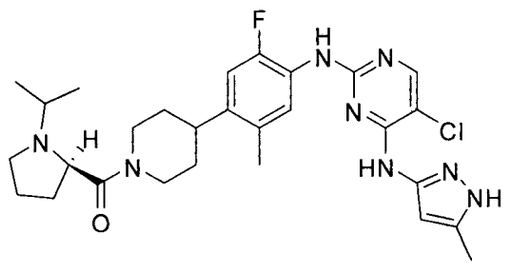
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (S)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-isopropil-piperidin-2-il)-metanona	ESMS *m/z* 569.3 ($M + H^+$).	0.012
	 (S)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(4-isopropil-morfolin-3-il)-metanona	ESMS *m/z* 571.3 ($M + H^+$).	0.029

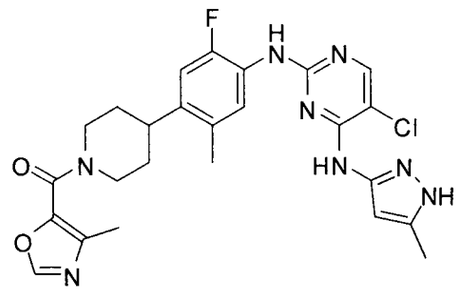
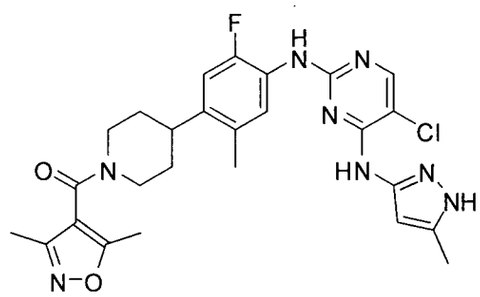
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(2,4-dimetil-oxazol-5-il)-metanona	ESMS *m/z* 539.2 ($M + H^+$).	0.027
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-((2S)-4-hidroxi-1-metil-pirrolidin-2-il)-metanona	ESMS *m/z* 543.2 ($M + H^+$).	0.175

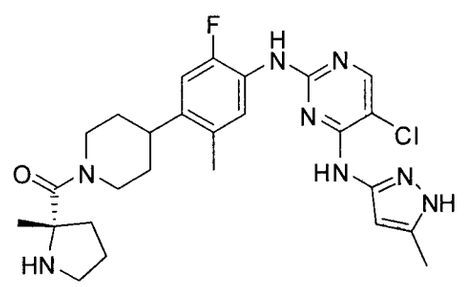
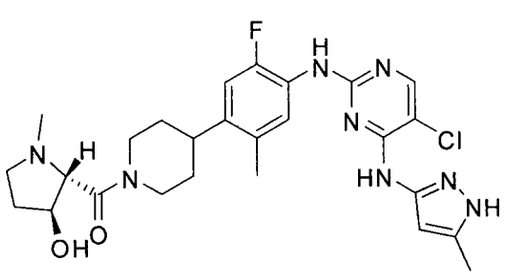
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1,3,5-trimetil-1H-pirazol-4-il)-metanona	ESMS *m/z* 552.2 ($M + H^+$).	0.025
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-metil-5-(trifluoro-metil)-1H-pirazol-4-il)-metanona	ESMS *m/z* 592.2 ($M + H^+$).	0.061

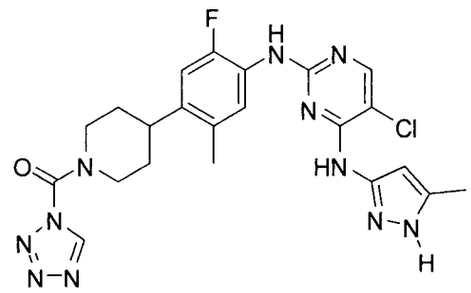
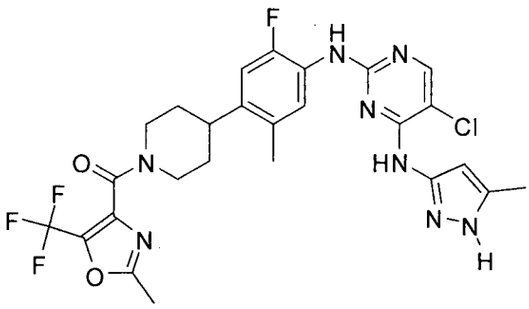
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 azetidin-3-il-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-metanona	^{1}H RMN (400 MHz, MeOD-d_4) δ 8.08 (s, 1H), 7.68 (d, 2H), 7.04 (d, 2H), 6.26 (s, 1H), 4.74-4.68 (m, 2H), 4.39-4.35 (m, 1H), 4.29-4.24 (m, 2H), 4.11 -4.07 (m, 1H), 3.74-3.71 (m, 1H), 3.25 - 3.24 (m, 1H), 3.07-3.04 (m, 1H), 2.87-2.80 (m, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 1.87-1.84 (m, 2H), 1.66-1.56 (m, 2H);	1.25

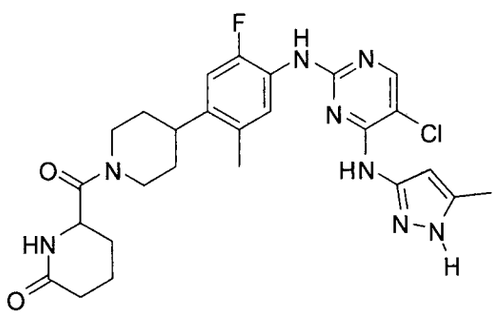
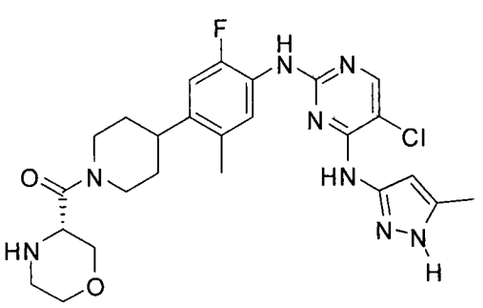
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
		ESMS *m/z* 499.2 ($M + H^+$).	
	 (S)-azetidin-2-il-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-metanona	ESMS m/z 499.2 (M + H+).	0.161
	 (R)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(1-metil-pirrolidin-2-il)-	ESMS *m/z* 523.3 ($M + H^+$).	0.013

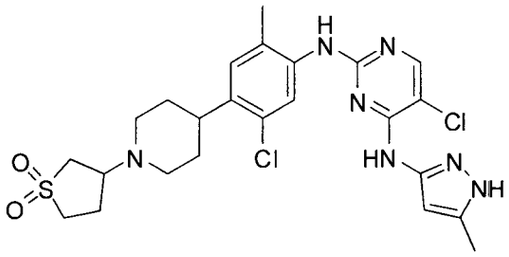
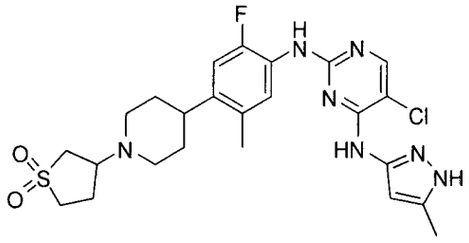
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	metanona		
	 (R)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-metil-pirrolidin-2-il)-metanona	ESMS *m/z* 527.2 ($M + H^+$).	0.021
	 (R)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-isopropil-pirrolidin-2-il)-metanona	ESMS *m/z* 555.3 ($M + H^+$).	0.048

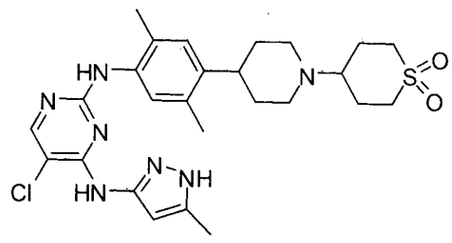
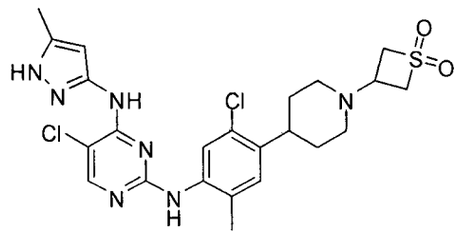
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(4-metil-oxazol-5-il)-metanona	ESMS *m/z* 525.2 ($M + H^+$).	0.035
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(3,5-dimetil-isoxazol-4-il)-metanona	ESMS *m/z* 539.2 ($M + H^+$).	0.018

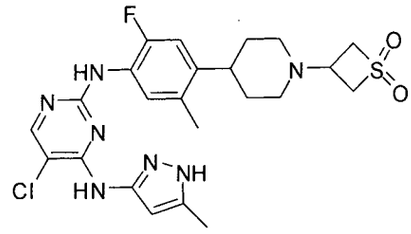
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (S)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(2-metil-pirrolidin-2-il)-metanona	ESMS *m/z* 527.2 ($M + H^+$).	0.091
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-((2S,3R)-3-hidroxi-1-metil-pirrolidin-2-il)-metanona	ESMS *m/z* 543.2 ($M + H^+$).	0.175

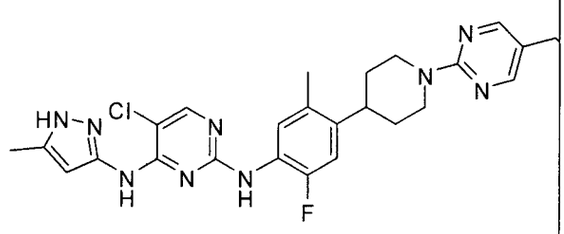
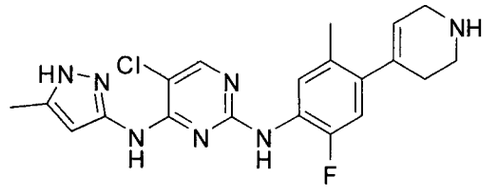
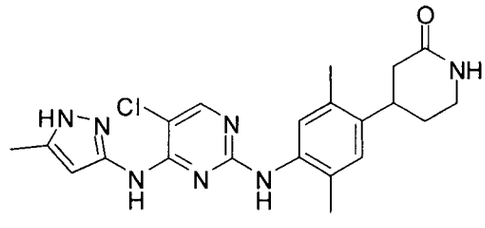
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1H-tetrazol-1-il)-metanona	ESMS *m/z* 512.2 ($M + H^+$).	0.139
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(2-metil-5-(trifluoro-metil)-oxazol-4-il)-metanona	ESMS *m/z* 593.2 ($M + H^+$).	0.069

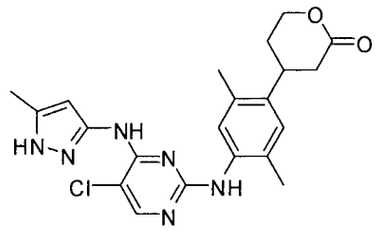
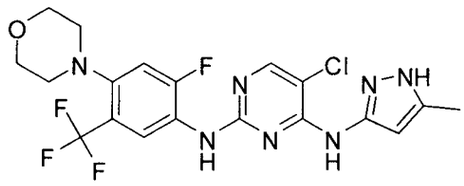
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 6-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-carbonil)-piperidin-2-ona	ESMS *m/z* 541.2 ($M + H^+$).	0.282
	 (S)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(morfolin-3-il)-metanona	ESMS *m/z* 529.2 ($M + H^+$).	0.071

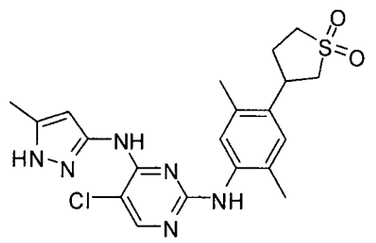
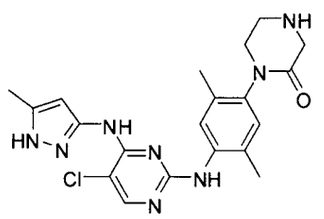
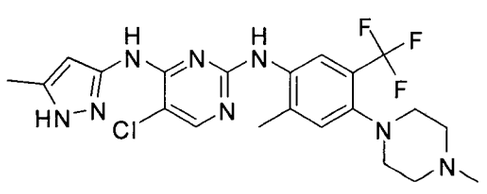
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N^2-(2-metil-5-cloro-4-(1-(tetrahidro-1,1-dioxido-3-tienil)-piperidin-4-il)-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 550.1 ($M + H^+$).	0.007
	 5-cloro-N^2-(2-fluoro-5-metil-4-(1-(tetrahidro-1,1-dioxido-3-tienil)-piperidin-4-il)-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 534.2 ($M + H^+$).	0.018

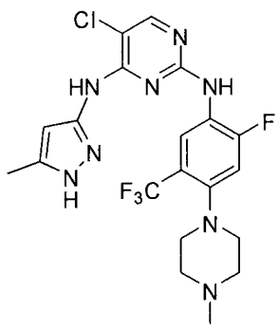
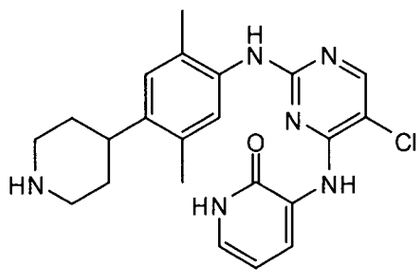
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(2,5-dimetil-4-(1-(tetrahidro-1,1-dioxido-2H-tiopiran-4-il))-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS m/z 544.2 ($M + H^+$).	0.258
	 5-cloro-N2-(2-cloro-5-metil-4-(1-(1,1-dioxido-3-tietanil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 536.1 ($M + H^+$).	0.016

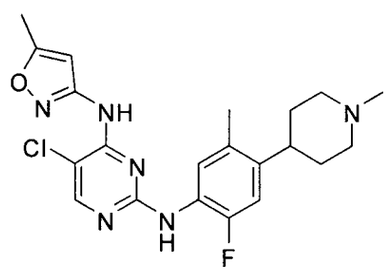
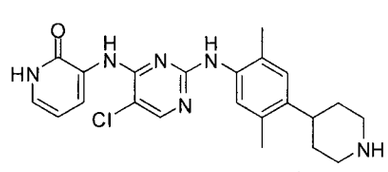
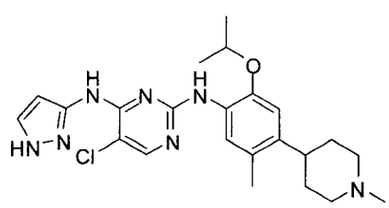
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(1,1-dioxido-3-tietanil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS m/z 520.2 ($M + H^+$). ^1H RMN (400 MHz, DMSO-d_6 + 1 gota D_2O) δ 8.02 (s, 1H), 7.37 (s, 1H), 7.02 (s, 1H), 6.23 (s, 1H), 4.28-4.22 (m, 2H), 4.12-4.07 (m, 2H), 3.22-3.18 (m, 1H), 2.95-2.92 (m, 2H), 2.68-2.62 (m, 1H), 2.22 (s, 3H), 2.13 (s, 3H), 2.07-2.01 (m, 2H), 1.71-1.55 (m, 4H).	0.018

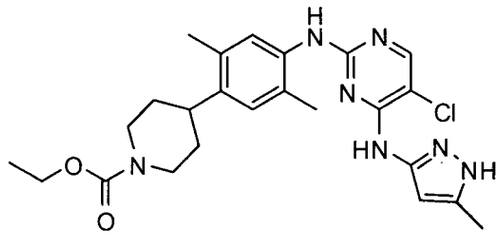
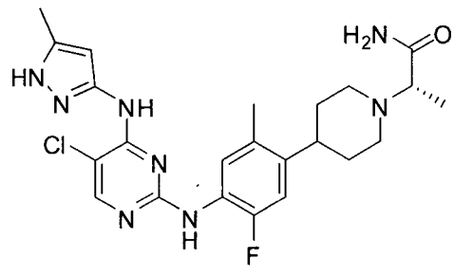
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(4-(1-(5-etil-pirimidin-2-il)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS m/z 522.2 (M + H+).	0.955
X	 5-cloro-N2-(2-fluoro-5-metil-4-(1,2,3,6-tetrahidro-piridin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 414.1 ($M + H^+$).	0.025
X	 4-(4-(5-cloro-4-(5-metil-1H-	ESMS *m/z* 426.2 ($M + H^+$).	0.009

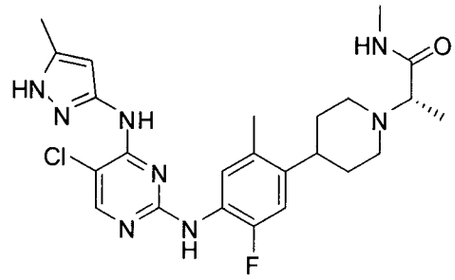
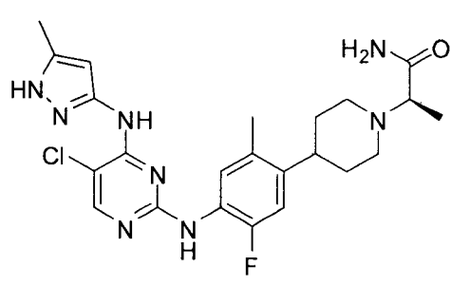
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-2-ona		
	 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-tetrahidro-2H-piran-2-ona	ESMS *m/z* 427.2 ($M + H^+$).	0.155
	 5-cloro-N2-(2-fluoro-4-morfolino-5-(trifluoro-metil)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS m/z 472.1 (M + H+).	0.091

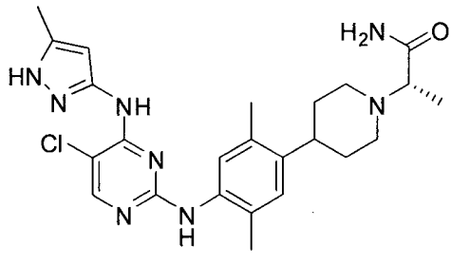
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N^2-[4-(1,1-dioxo-tetrahidro-1□^{6}-tiofen-3-il)-2,5-dimetil-fenil]-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 447.1 ($M + H^+$).	0.012
	 1-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperazin-2-ona	ESMS *m/z* 427.2 ($M + H^+$).	1.65
	 5-cloro-N4-(5-metil-1H-pirazol-3-	ESMS *m/z* 481.2 ($M + H^+$)	0.040

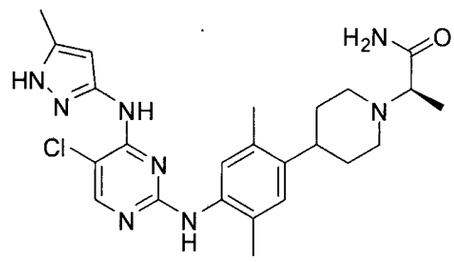
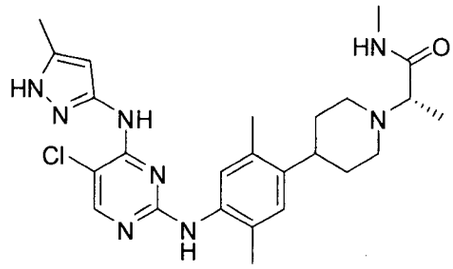
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	il)-N2-(2-metil-4-(4-metil-piperazin-1-il)-5-(trifluoro-metil)-fenil)-pirimidin-2,4-diamina		
	 5-cloro-N2-(2-fluoro-4-(4-metil-piperazin-1-il)-5-(trifluoro-metil)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS m/z 485.2 ($M + H^+$).	0.075
	 3-(5-cloro-2-(2,5-dimetil-4-(piperidin-4-il)-fenil-amino)-pirimidin-4-il-amino)-piridin-2(1H)-	ESMS *m/z* 425.2 ($M + H^+$).	0.062

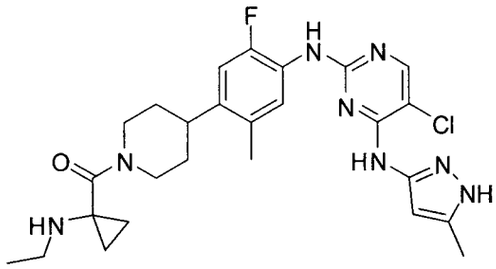
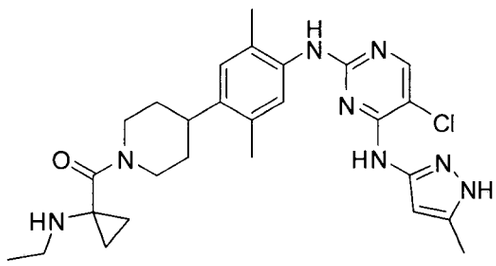
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	ona		
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil)-N4-(5-metil-isoxazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 431.2 ($M + H^+$).	0.073
	 3-(5-cloro-2-(2,5-dimetil-4-(piperidin-4-il)-fenil-amino)-pirimidin-4-il-amino)-piridin-2(1H)-ona	ESMS *m/z* 425.2 ($M + H^+$).	
		ESMS *m/z* 456.2 ($M + H^+$).	0.332

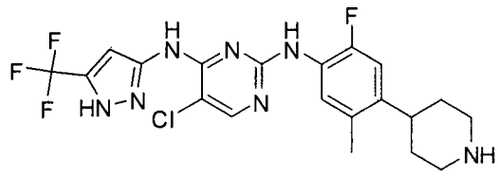
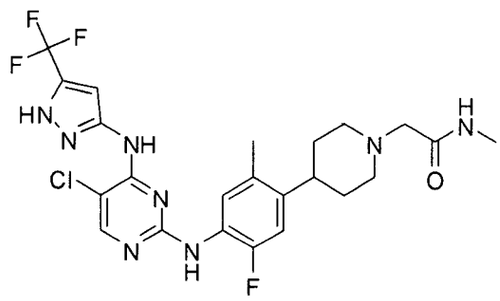
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	5-cloro-N2-(2-isopropoxi-5-metil-4-(1-metil-piperidin-4-il)-fenil)-N4-(1H-pirazol-3-il)-pirimidin-2,4-diamina		
	 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-carboxilato de etilo	ESMS *m/z* 438.9 ($M + H^+$).	0.013
	 (S)-2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propanamida	ESMS *m/z* 487.2 ($M + H^+$)	0.056

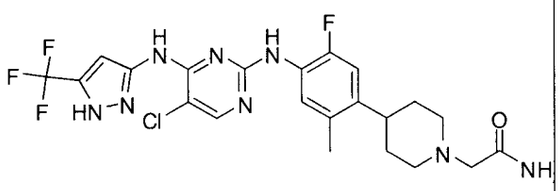
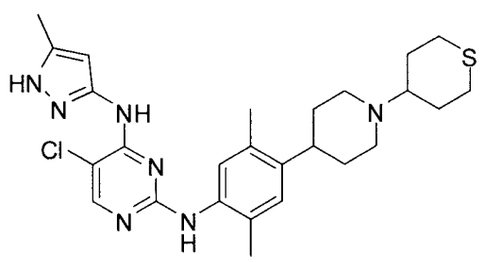
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (S)-2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-N-metil-propanamida	ESMS *m/z* 501.2 ($M + H^+$); ^{1}H RMN (MeOD-d_4) δ 8.25 (s, 1H), 7.56 (m, 1H), 7.20 (d, 1H), 6.46 (s, 1H), 3.97 (m, 1H), 3.79 (m, 1H), 3.62 (m, 1H), 3.25 (m, 3H), 2.84 (s, 3H), 2.40 (d, 6H), 2.08 (m, 4H), 1.62 (m, 3H).	0.033
		ESMS *m/z* 487.2 ($M + H^+$); ^{1}H RMN (MeOD-d_4) δ 8.22 (s, 1H), 7.61 (t,	0.038

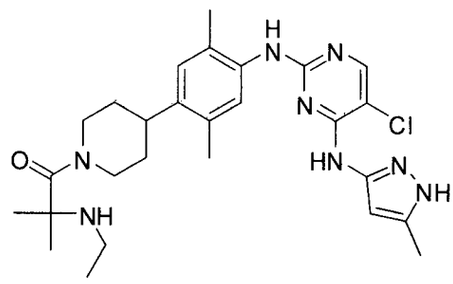
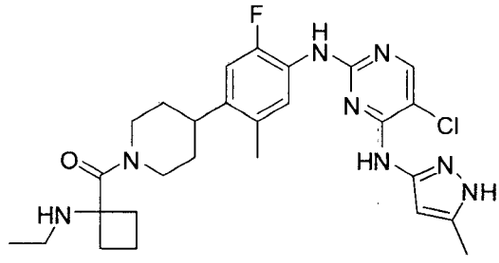
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	(R)-2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propanamida	1H), 7.18 (d, 1H), 6.40 (s, 1H), 3.79 (m, 1H), 3.65 (m, 1H), 3.54 (m, 1H), 3.22 (m, 3H), 2.39 (d, 6H), 2.08 (m, 4H), 1.66 (d, 3H)	
	 (S)-2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-propanamida	ESMS *m/z* 483.2 ($M + H^+$)	0.007

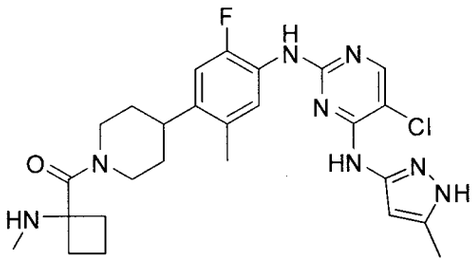
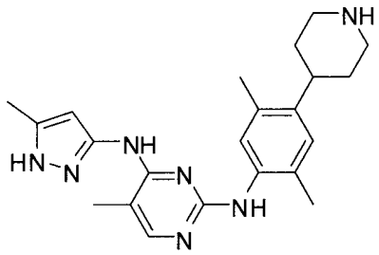
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (R)-2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-propanamida	ESMS *m/z* 483.2 ($M + H^+$)	0.006
	 (S)-2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-propanamida	ESMS *m/z* 497.2 ($M + H^+$)	0.01

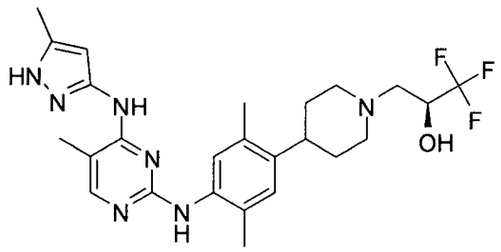
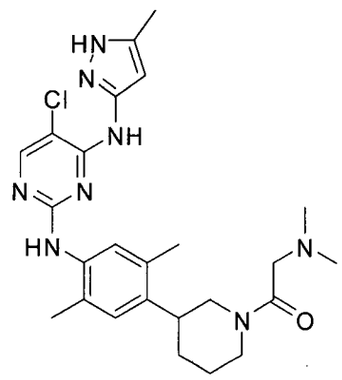
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-(etil-amino)-ciclopropil)-metanona	ESMS *m/z* 527.2 ($M + H^+$); ^{1}H RMN (MeOD-d_4) δ 8.24 (s, 1H), 7.49 (d, 1H), 7.23 (d, 1H), 6.47 (s, 1H), 4.52 (d, 2H), 3.26 (q, 2H), 3.18 (m, 3H), 2.40 (s, 6H), 1.91(d, 2 H), 1.71(m, 2H), 1.49 (m, 3H), 1.39 (t, 3H).	0.004
	 (4-(4-(5-cloro-4-(5-metil-1H-	ESMS *m/z* 523.3 ($M + H^+$)	0.003

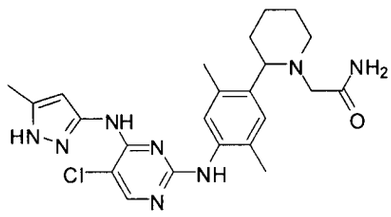
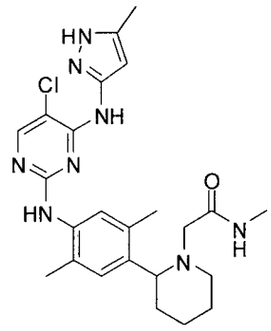
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(1-(etil-amino)-ciclopropil)-metanona		
	 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-(trifluoro-metil)-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 470.1 ($M + H^+$)	0.067
	 2-(4-(4-(5-cloro-4-(5-(trifluoro-metil)-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-N-metil-	ESMS *m/z* 541.2 ($M + H^+$)	0.069

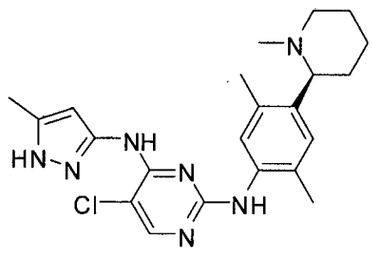
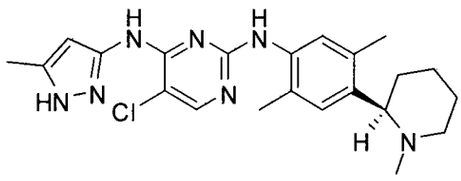
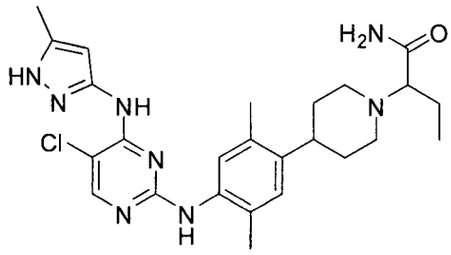
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	acetamida		
	 2-(4-(4-(5-cloro-4-(5-(trifluoro-metil)-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-acetamida	ESMS *m/z* 527.2 ($M + H^+$)	0.049
	 5-cloro-N2-(2,5-dimetil-4-(1-(tetrahidro-2H-tiopiran-4-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 512.2 ($M + H^+$)	0.008

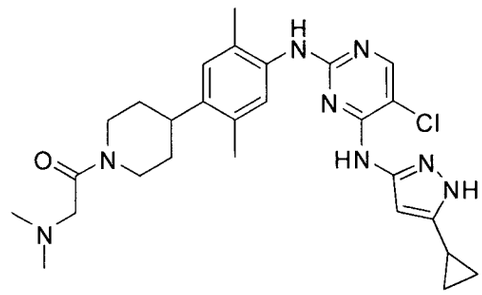
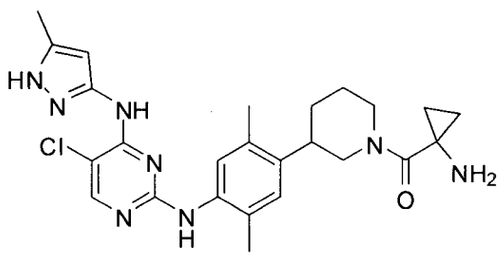
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(etil-amino)-2-metil-propan-1-ona	ESMS *m/z* 525.3 ($M + H^+$)	0.005
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-(etil-amino)-ciclobutil)-metanona	ESMS *m/z* 541.3 ($M + H^+$)	0.084

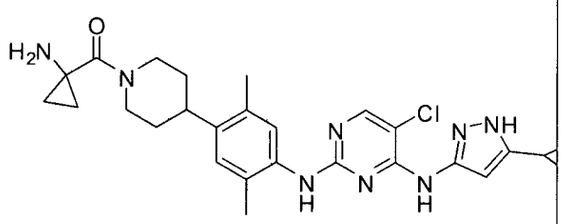
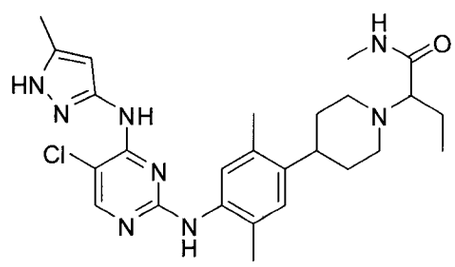
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-(metil-amino)-ciclobutil)-metanona	ESMS *m/z* 527.2 ($M + H^+$)	0.08
	 N2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-5-metil-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 392.2 ($M + H^+$)	3.229

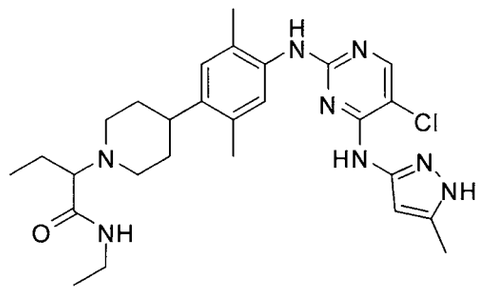
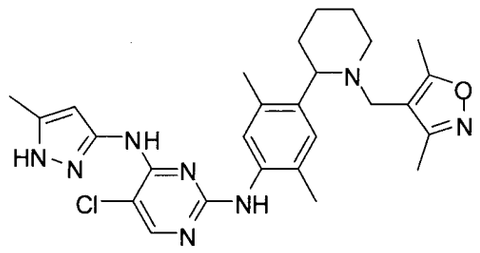
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (S)-3-(4-(2,5-dimetil-4-(5-metil-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol	ESMS *m/z* 504.3 (M + H^+)	0.12
	 1-(3-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona	ESMS *m/z* 497.2 (M + H^+)	0.025

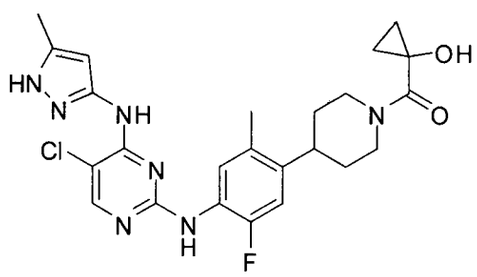
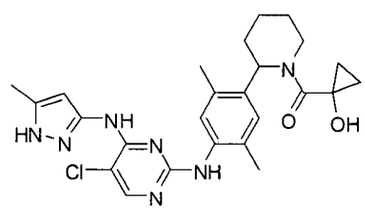
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 2-(2-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-acetamida	ESMS *m/z* 469.2 ($M + H^+$)	0.024
	 2-(2-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida	ESMS *m/z* 483.2 ($M + H^+$)	0.019

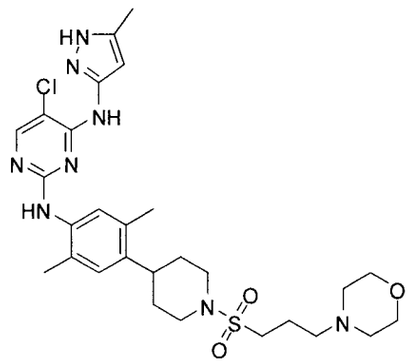
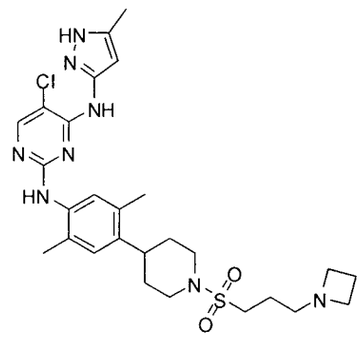
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (S)-5-cloro-N2-(2,5-dimetil-4-(1-metil-piperidin-2-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 426.2 ($M + H^+$)	
	 (R)-5-cloro-N2-(2,5-dimetil-4-(1-metil-piperidin-2-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 426.2 ($M + H^+$)	
	 2-(4-(4-(5-cloro-4-(5-metil-1H-	ESMS *m/z* 497.2 ($M + H^+$)	0.009

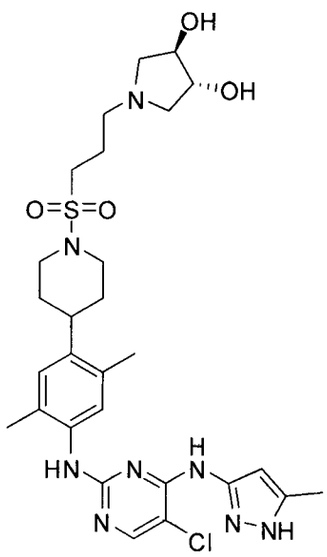
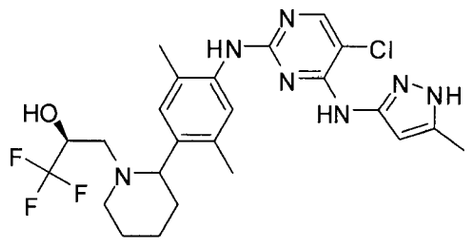
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-butanamida		
	 1-(4-(4-(5-cloro-4-(5-ciclopropil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona	ESMS *m/z* 523.3 ($M + H^+$)	0.012
	 (1-amino-ciclopropil)-(3-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-	ESMS *m/z* 495.2 ($M + H^+$)	0.095

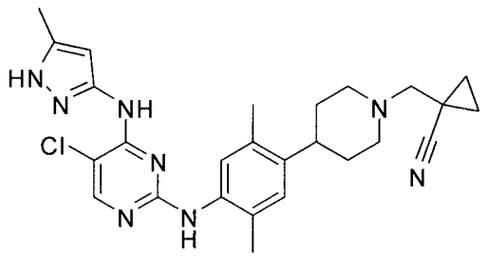
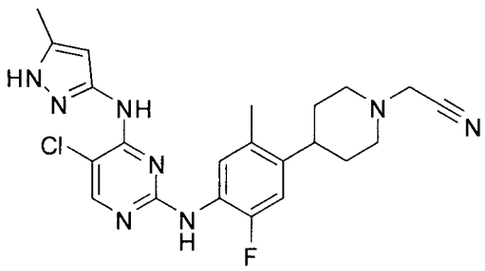
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	dimetil-fenil)-piperidin-1-il)-metanona		
	 (1-amino-ciclopropil)-(4-(4-(5-cloro-4-(5-ciclopropil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-metanona	ESMS *m/z* 521.2 ($M + H^+$)	0.019
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-butanamida	ESMS *m/z* 511.3 ($M + H^+$)	0.007

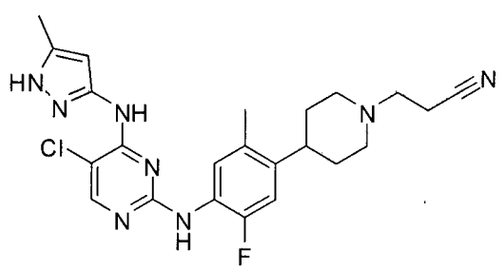
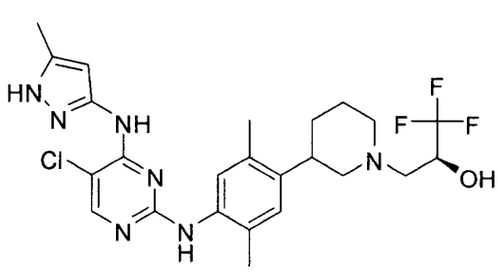
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-etil-butanamida	ESMS *m/z* 525.3 ($M + H^+$)	0.007
	 5-cloro-N2-(4-(1-((3,5-dimetil-isoxazol-4-il)-metil)-piperidin-2-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 521.2 ($M + H^+$)	0.113

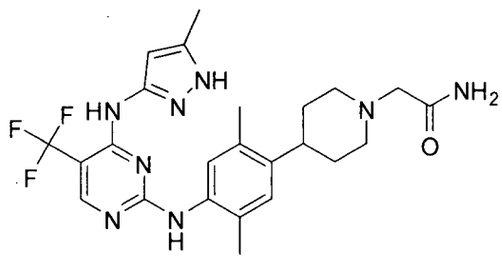
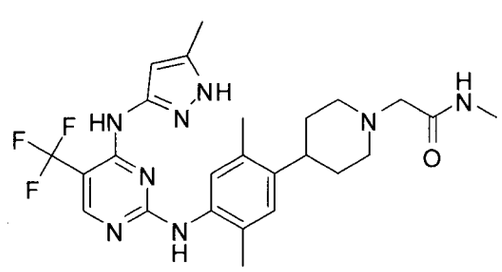
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-hidroxi-ciclopropil)-metanona	ESMS *m/z* 500.2 ($M + H^+$)	0.021
	 (2-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(1-hidroxi-ciclopropil)-metanona	ESMS *m/z* 496.2 ($M + H^+$)	0.076

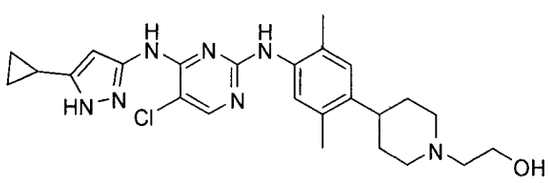
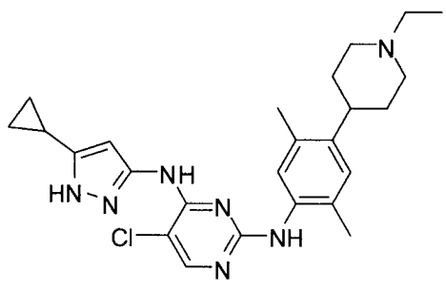
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(2,5-dimetil-4-(1-(3-morfolinopropil-sulfonil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 603.3 ($M + H^+$)	0.013
	 N2-(4-(1-(3-(azetidin-1-il)-propil-sulfonil)-piperidin-4-il)-2,5-dimetil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 573.2 ($M + H^+$)	0.027

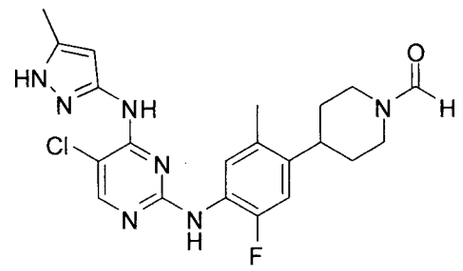
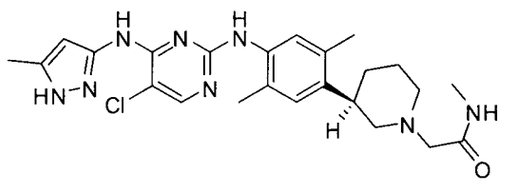
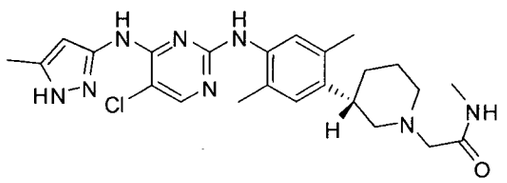
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (3R,4R)-1-(3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il-sulfonil)-propil)-pirrolidin-3,4-diol	ESMS *m/z* 619.3 ($M + H^+$)	0.37
	 (2S)-3-(2-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-	ESMS *m/z* 524.2 ($M + H^+$)	0.21

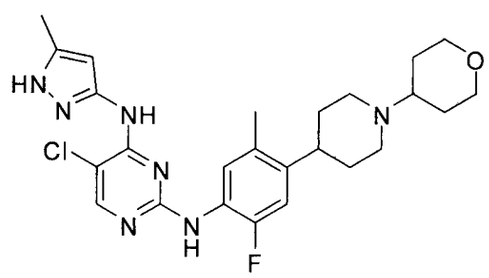
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	piperidin-1-il)-1,1,1-trifluoro-propan-2-ol		
	 1-((4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-metil)-ciclopropan-carbonitrilo	ESMS *m/z* 491.2 ($M + H^+$)	0.022
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-acetonitrilo	ESMS *m/z* 455.2 ($M + H^+$)	0.077

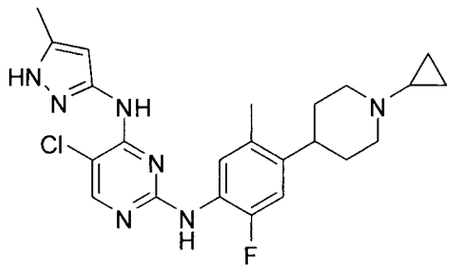
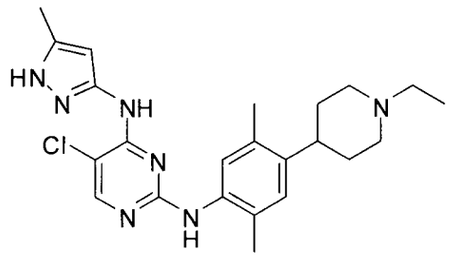
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propano-nitrilo	ESMS *m/z* 469.2 ($M + H^+$)	0.036
	 (2S)-3-(3-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol	ESMS *m/z* 524.2 ($M + H^+$)	0.046

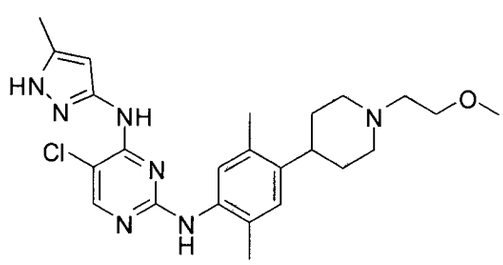
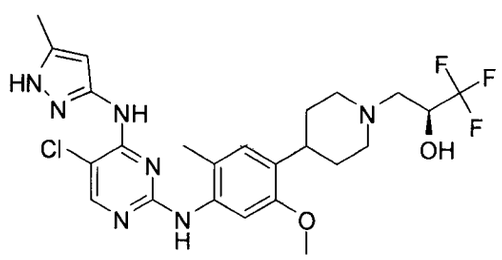
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 2-(4-(2,5-dimetil-4-(4-(5-metil-1H-pirazol-3-il-amino)-5-(trifluoro-metil)-pirimidin-2-il-amino)-fenil)-piperidin-1-il)-acetamida	ESMS *m/z* 503.2 ($M + H^+$); ^{1}H RMN (MeOD-d_4) δ 8.23 (s, 1H), 7.26 (s, 1H), 7.20 (s, 1H), 6.20 (s, 1H), 4.00 (s, 2H), 3.75 (d, 2H), 3.55 (m, 2H), 3.14 (m, 1H), 2.36 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 2.08 (m, 4H).	0.02
	 2-(4-(2,5-dimetil-4-(4-(5-metil-1H-	ESMS *m/z* 517.3 ($M + H^+$)	0.015

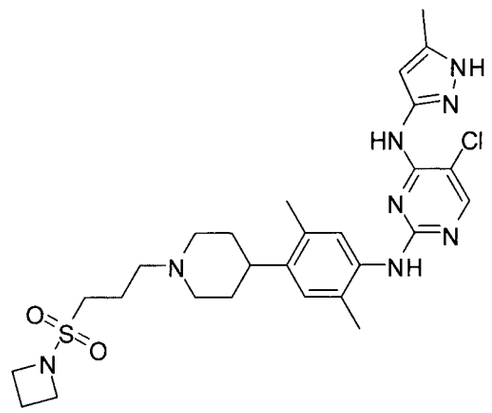
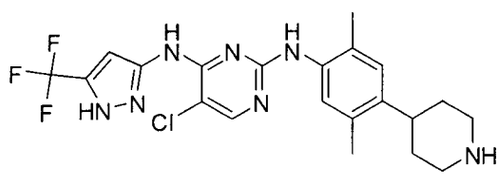
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	pirazol-3-il-amino)-5-(trifluoro-metil)-pirimidin-2-il-amino)-fenil)-piperidin-1-il)-N-metil-acetamida		
	 2-(4-(4-(5-cloro-4-(5-ciclopropil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-etanol	ESMS *m/z* 482.2 ($M + H^+$)	0.016
	 5-cloro-N4-(5-ciclopropil-1H-pirazol-3-il)-N2-(4-(1-etil-piperidin-4-il)-2,5-dimetil-fenil)-pirimidin-2,4-diamina	ESMS *m/z* 466.2 ($M + H^+$)	0.019

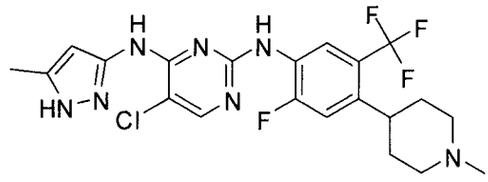
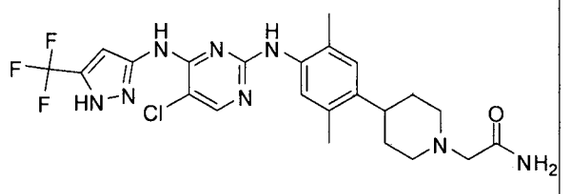
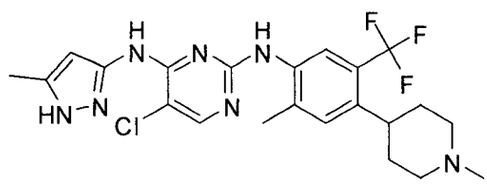
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-carbaldehído	ESMS *m/z* 444.2 ($M + H^+$)	0.03
	 (R)-2-(3-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida	ESMS *m/z* 483.2 ($M + H^+$)	0.026
	 (S)-2-(3-(4-(5-cloro-4-(5-metil-1H-	ESMS *m/z* 483.2 ($M + H^+$)	0.01

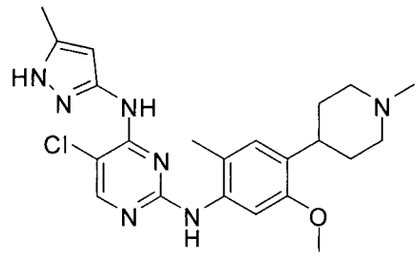
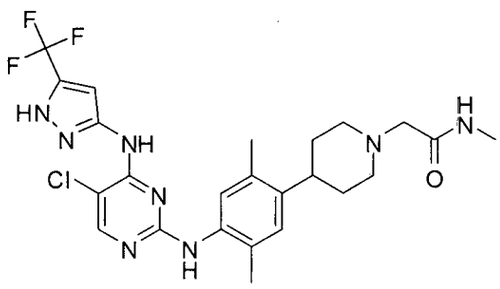
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida		
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(tetrahidro-2H-piran-4-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 500.2 ($M + H^+$); ^{1}H RMN (DMSO-d_6, 400 MHz) δ 12.08 (br, 1H), 9.58 (br, 1H), 8.65 (d, *J* = 28.4 Hz, 1H), 8.02 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 12.4 Hz, 1H), 6.08 (br, 1H), 3.89 (dd, *J* = 10.8, 3.6 Hz, 2H), 3.28 (t, *J* = 10.4 Hz, 2H), 2.99 (d, *J* =	0.027

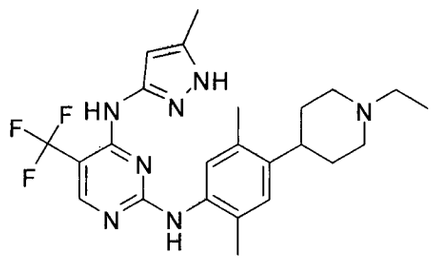
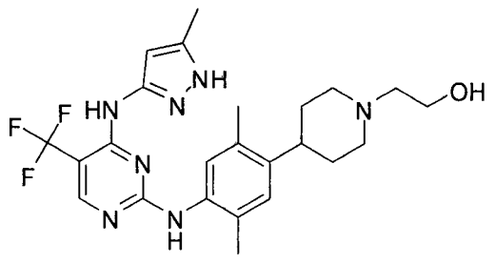
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
		10.8 Hz, 2H), 2.64-2.43 (m, 2H), 2.24-2.15 (m, 8H), 1.71-1.40 (m, 8H)	
	 5-cloro-N2-(4-(1-ciclopropil-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 456.2 ($M + H^+$)	0.032
	 5-cloro-N2-(4-(1-etil-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-	ESMS *m/z* 440.2 ($M + H^+$)	0.009

	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	1H-pirazol-3-il)-pirimidin-2,4-diamina		
	 5-cloro-N2-(4-(1-(2-metoxi-etil)-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 470.2 ($M + H^+$)	0.013
	 (S)-3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2-metoxi-5-metil-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol	ESMS *m/z* 540.2 ($M + H^+$)	0.012

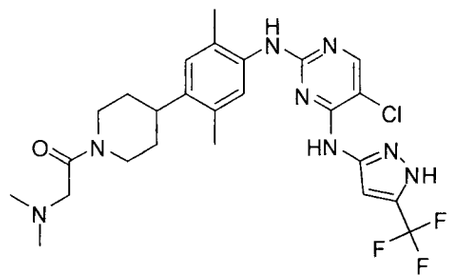
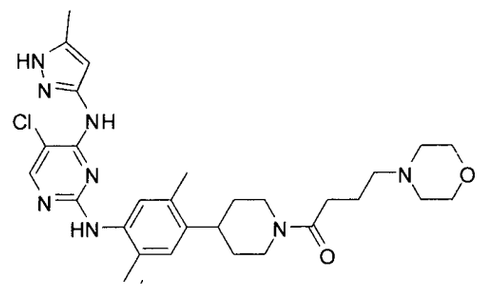
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 N2-(4-(1-(3-(azetidin-1-il-sulfonil)-propil)-piperidin-4-il)-2,5-dimetil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 573.2 ($M + H^+$)	0.04
	 5-cloro-N2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-N4-(5-(trifluoro-metil)-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 466.2 ($M + H^+$)	0.047

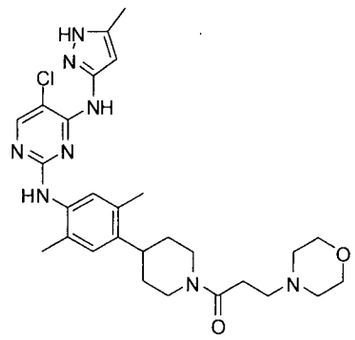
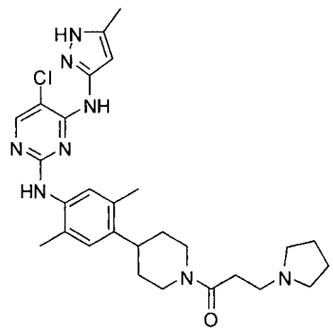
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(2-fluoro-4-(1-metil-piperidin-4-il)-5-(trifluoro-metil)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 484.2 ($M + H^+$)	0.047
	 2-(4-(4-(5-cloro-4-(5-(trifluoro-metil)-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-acetamida	ESMS *m/z* 523.2 ($M + H^+$)	0.034
	 5-cloro-N4-(5-metil-1H-pirazol-3-il)-N2-(2-metil-4-(1-metil-piperidin-	ESMS *m/z* 480.2 ($M + H^+$)	0.026

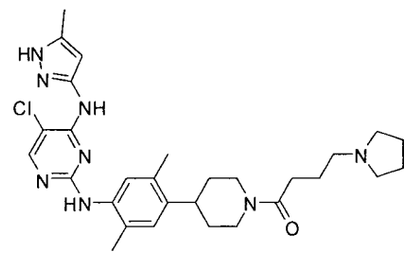
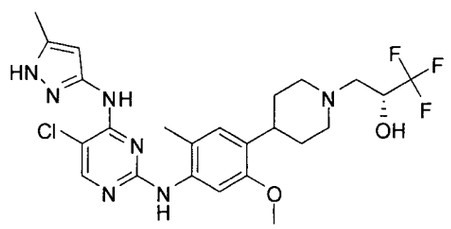
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	4-il)-5-(trifluoro-metil)-fenil)-pirimidin-2,4-diamina		
	 5-cloro-N2-(5-metoxi-2-metil-4-(1-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 442.2 ($M + H^+$)	0.009
	 2-(4-(4-(5-cloro-4-(5-(trifluoro-metil)-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida	ESMS *m/z* 537.2 ($M + H^+$)	0.037

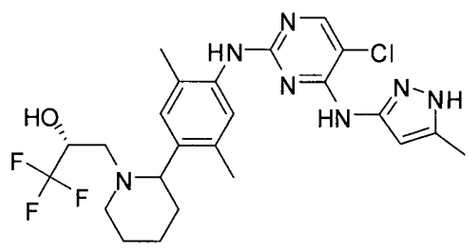
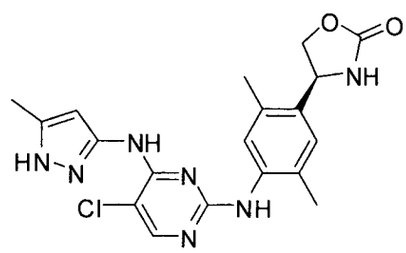
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 N2-(4-(1-etil-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-5-(trifluoro-metil)-pirimidin-2,4-diamina	ESMS *m/z* 474.3 ($M + H^+$)	0.034
	 2-(4-(2,5-dimetil-4-(4-(5-metil-1H-pirazol-3-il-amino)-5-(trifluoro-metil)-pirimidin-2-il-amino)-fenil)-piperidin-1-il)-etanol	ESMS *m/z* 490.2 ($M + H^+$)	0.038

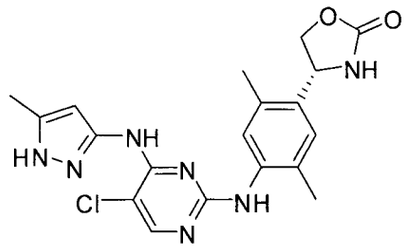
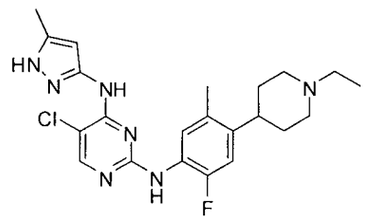
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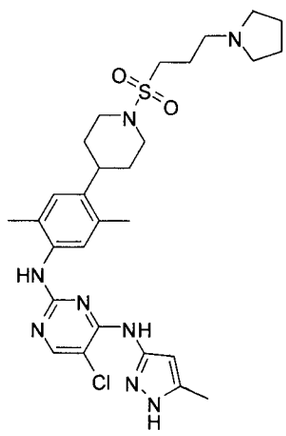
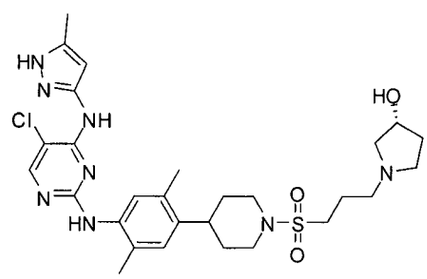
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 1-(4-(4-(5-cloro-4-(5-(trifluoro-metil)-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona	ESMS *m/z* 551.2 ($M + H^+$)	0.036
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-4-morfolinobutan-1-ona	ESMS *m/z* 567.3 ($M + H^+$)	0.02

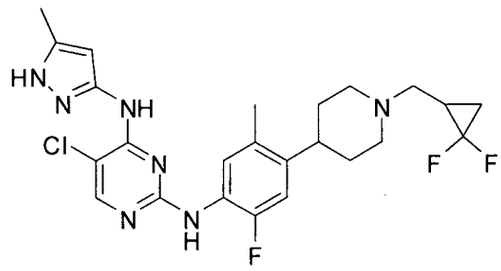
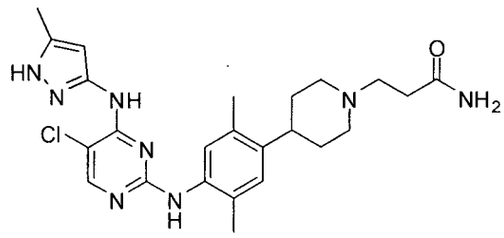
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-3-morfolino-propan-1-ona	ESMS *m/z* 553.3 ($M + H^+$)	0.017
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-3-(pirrolidin-1-il)-propan-1-ona	ESMS *m/z* 537.3 ($M + H^+$)	0.061

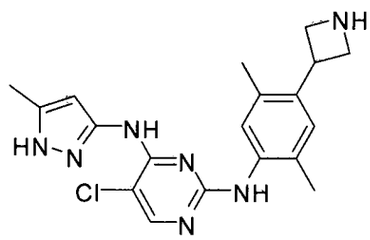
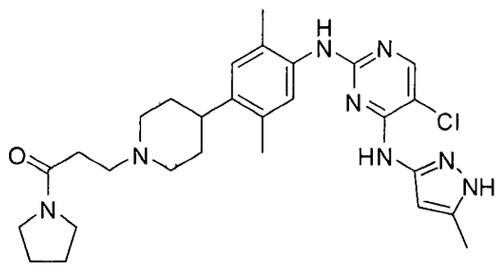
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-4-(pirrolidin-1-il)-butan-1-ona	ESMS *m/z* 551.3 ($M + H^+$)	0.123
	 (R)-3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2-metoxi-5-metil-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol	ESMS *m/z* 540.2 ($M + H^+$)	0.023

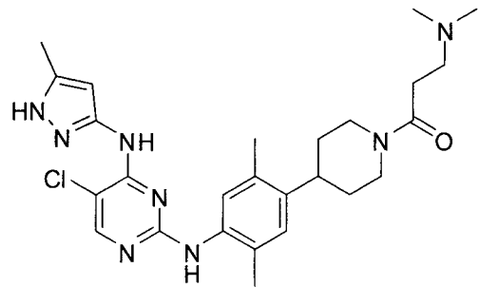
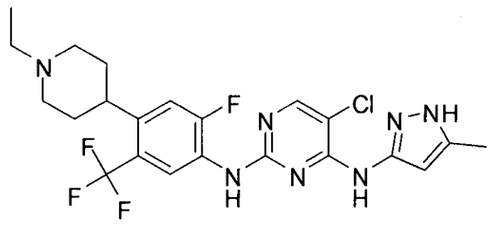
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (2R)-3-(2-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol	ESMS *m/z* 524.2 ($M + H^+$)	0.211
	 (S)-4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-oxazolidin-2-ona	ESMS *m/z* 414.1 ($M + H^+$)	0.04

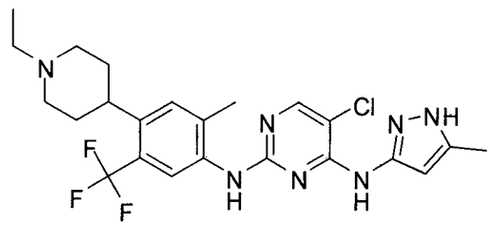
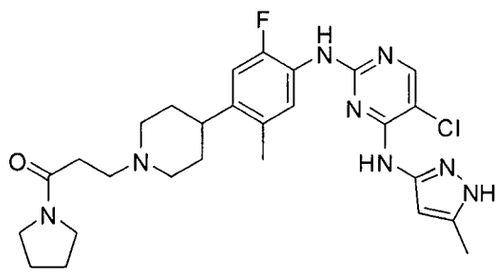
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (R)-4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-oxazolidin-2-ona	ESMS *m/z* 414.1 ($M + H^+$)	0.05
	 5-cloro-N2-(4-(1-etil-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 444.2 ($M + H^+$); ^{1}H RMN (DMSO-d_6) δ 8.01 (s, 1H), 7.35 (m, 1H), 7.02 (d, 1H), 6.22 (s,1H), 2.97 (d, 2H), 2.62 (m, 1H), 2.34 (q, 2H), 2.21 (s, 3H), 2.13 (s, 3H), 1.98 (t,	0.020

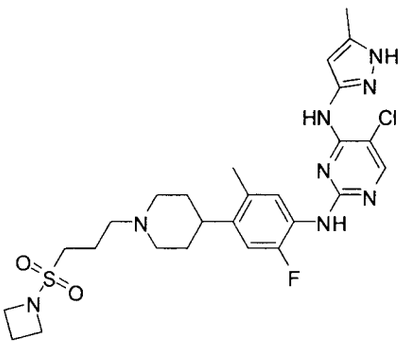
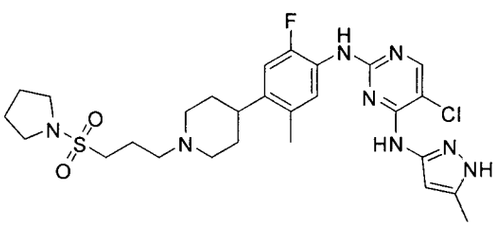
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
		2H), 1.64 (m, 4H), 1.01 (t, 3H).	
	 5-cloro-N2-(2,5-dimetil-4-(1-(3-(pirrolidin-1-il)-propil-sulfonil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 587.3 ($M + H^+$)	0.054
	 (R)-1-(3-(4-(4-(5-cloro-4-(5-metil-	ESMS *m/z* 603.3 ($M + H^+$)	0.073

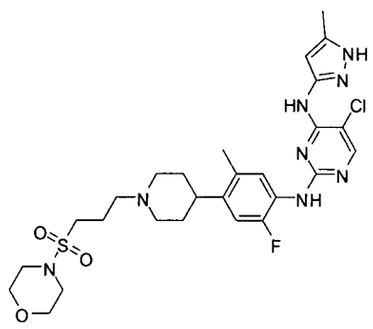
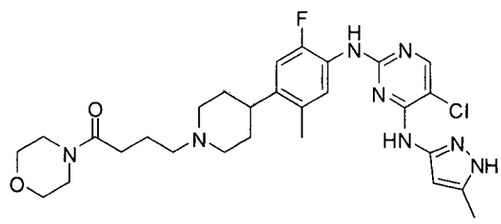
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il-sulfonil)-propil)-pirrolidin-3-ol		
	 5-cloro-N2-(4-(1-((2,2-difluoro-ciclopropil)-metil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 506.2 ($M + H^+$)	0.063
	 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-	ESMS *m/z* 483.2 ($M + H^+$)	0.059

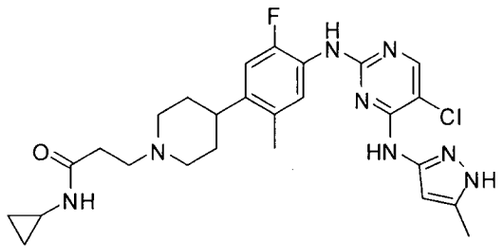
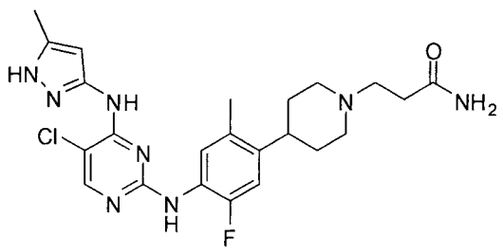
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	1-il)-propanamida		
	 N2-(4-(azetidin-3-il)-2,5-dimetil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 384.2 ($M + H^+$)	0.41
	 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-1-(pirrolidin-1-il)-propan-1-ona	ESMS *m/z* 537.3 ($M + H^+$)	0.039

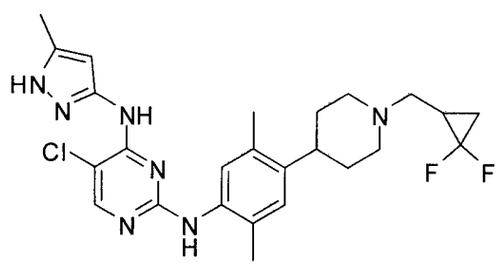
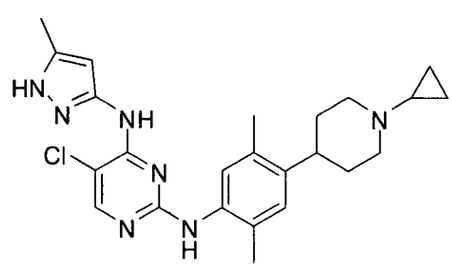
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-3-(dimetil-amino)-propan-1-ona	ESMS *m/z* 511.3 ($M + H^+$)	0.073
	 5-cloro-N2-(4-(1-etil-piperidin-4-il)-2-fluoro-5-(trifluoro-metil)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 498.2 ($M + H^+$)	0.102

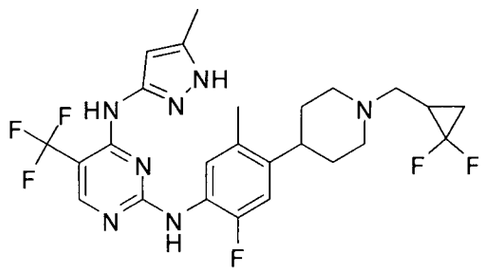
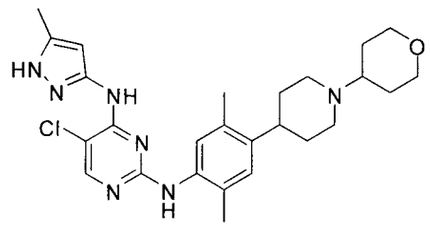
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(4-(1-etil-piperidin-4-il)-2-metil-5-(trifluoro-metil)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 494.2 ($M + H^+$)	0.068
	 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-1-(pirrolidin-1-il)-propan-1-ona	ESMS *m/z* 541.3 ($M + H^+$)	0.06

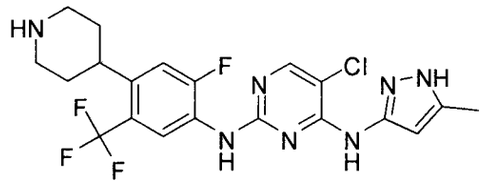
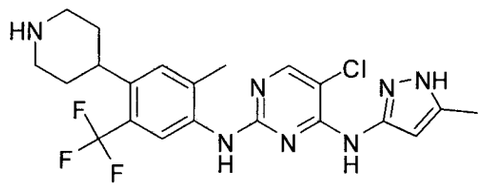
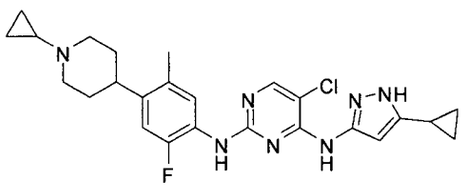
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 N2-(4-(1-(3-(azetidin-1-il-sulfonil)-propil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 577.2 ($M + H^+$)	0.076
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(3-(pirrolidin-1-il-sulfonil)-propil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 591.2 ($M + H^+$)	0.084

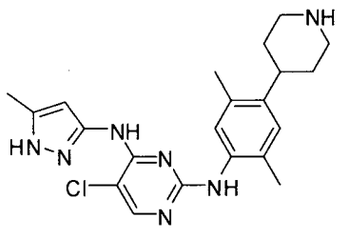
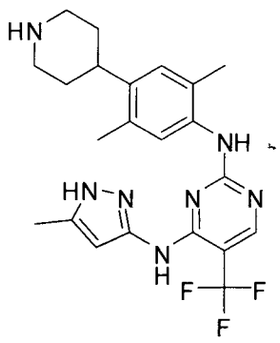
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(3-(morfolino-sulfonil)-propil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 607.2 ($M + H^+$)	0.077
	 4-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-1-morfolinobutan-1-ona	ESMS *m/z* 571.3 ($M + H^+$)	0.058

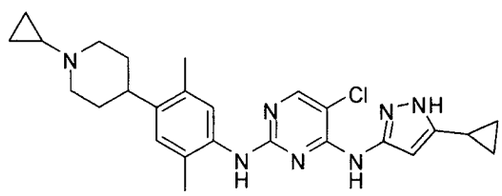
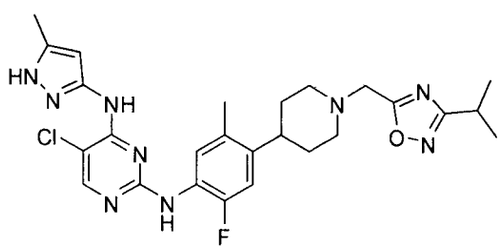
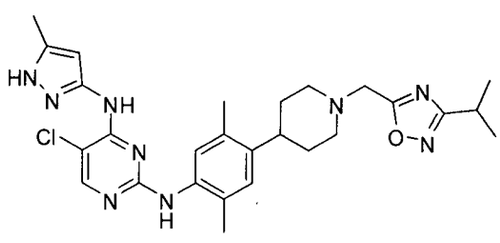
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-N-ciclopropil-propanamida	ESMS *m/z* 527.2 ($M + H^+$)	0.062
	 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propanamida	ESMS *m/z* 487.2 ($M + H^+$)	0.14

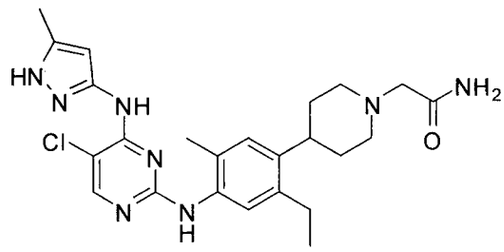
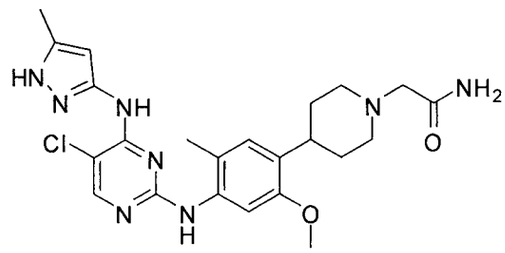
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(4-(1-((2,2-difluoro-ciclopropil)-metil)-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 502.2 ($M + H^+$)	0.032
	 5-cloro-N2-(4-(1-ciclopropil-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 452.2 ($M + H^+$)	0.025

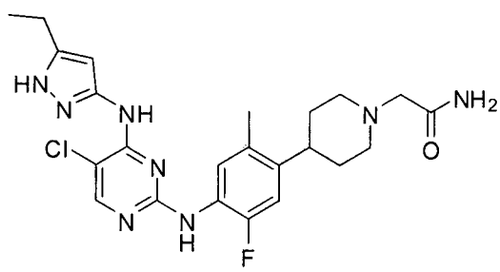
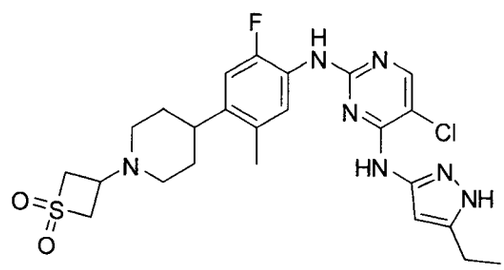
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 N2-(4-(1-((2,2-difluoro-ciclopropil)-metil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-5-(trifluoro-metil)-pirimidin-2,4-diamina	ESMS *m/z* 540.2 ($M + H^+$)	0.052
	 5-cloro-N2-(2,5-dimetil-4-(1-(tetrahidro-2H-piran-4-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 496.3 ($M + H^+$)	0.014

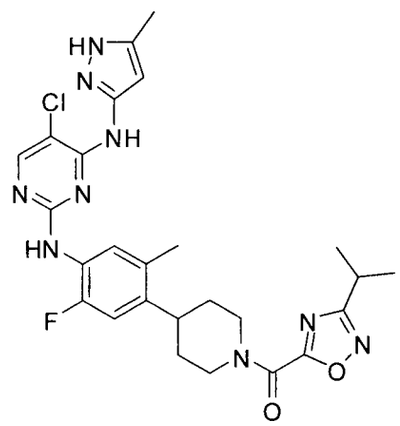
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(2-fluoro-4-(piperidin-4-il)-5-(trifluoro-metil)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 470.1 ($M + H^+$)	0.075
	 5-cloro-N4-(5-metil-1H-pirazol-3-il)-N2-(2-metil-4-(piperidin-4-il)-5-(trifluoro-metil)-fenil)-pirimidin-2,4-diamina	ESMS *m/z* 466.2 ($M + H^+$)	0.07
	 5-cloro-N4-(5-ciclopropil-1H-pirazol-3-il)-N2-(4-(1-ciclopropil-piperidin-4-il)-2-fluoro-5-metil-	ESMS *m/z* 482.2 ($M + H^+$)	0.228

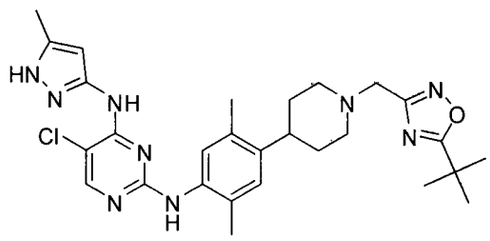
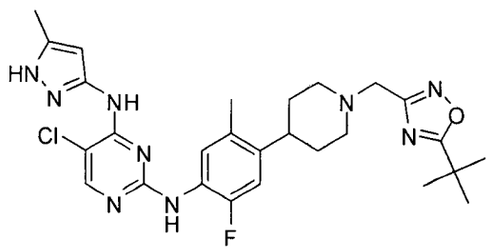
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	fenil)-pirimidin-2,4-diamina		
	 5-cloro-N2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 412.2 ($M + H^+$)	0.044
	 N2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-5-(trifluoro-metil)-pirimidin-2,4-diamina	ESMS *m/z* 446.2 ($M + H^+$)	0.064

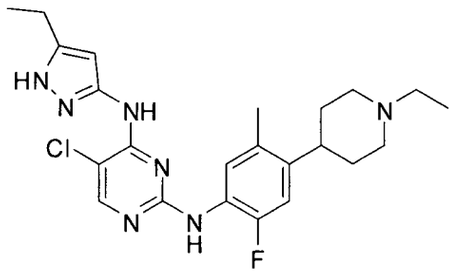
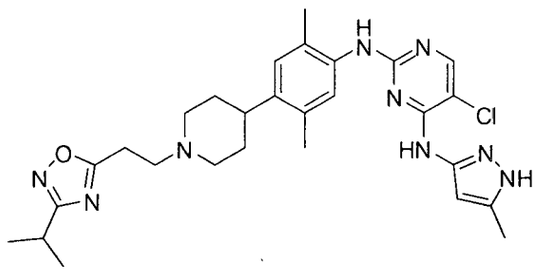
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N4-(5-ciclopropil-1H-pirazol-3-il)-N2-(4-(1-ciclopropil-piperidin-4-il)-2,5-dimetil-fenil)-pirimidin-2,4-diamina	ESMS *m/z* 478.2 ($M + H^+$)	0.026
	 5-cloro-N2-(2-fluoro-4-(1-((3-isopropil-1,2,4-oxadiazol-5-il)-metil)-piperidin-4-il)-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 540.2 ($M + H^+$)	0.064
		ESMS *m/z* 536.3 ($M + H^+$)	0.018

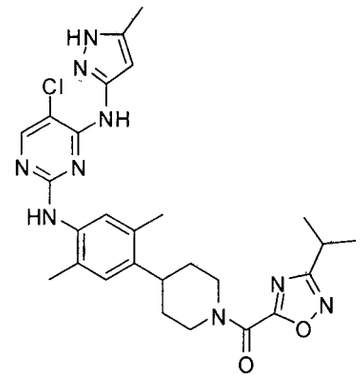
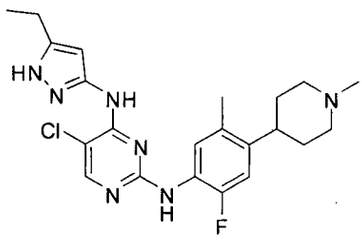
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	5-cloro-N2-(4-(1-((3-isopropil-1,2,4-oxadiazol-5-il)-metil)-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina		
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2-etil-5-metil-fenil)-piperidin-1-il)-acetamida	ESMS *m/z* 483.2 ($M + H^+$)	0.027
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2-metoxi-5-metil-fenil)-	ESMS *m/z* 485.2 ($M + H^+$)	0.019

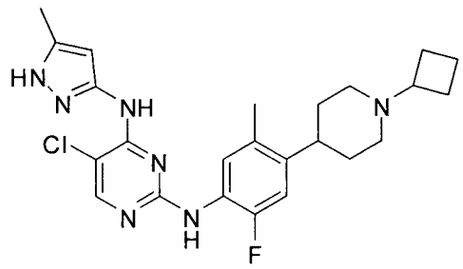
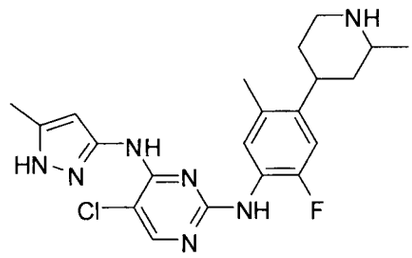
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	piperidin-1-il)-acetamida		
	 2-(4-(4-(5-cloro-4-(5-etil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-acetamida	ESMS *m/z* 487.2 ($M + H^+$)	0.033
	 5-cloro-N2-{4-[1-(1,1-dioxo-1λ6-tietan-3-il)-piperidin-4-il]-2-fluoro-5-metil-fenil}-N4-(5-etil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 534.2 ($M + H^+$)	0.021

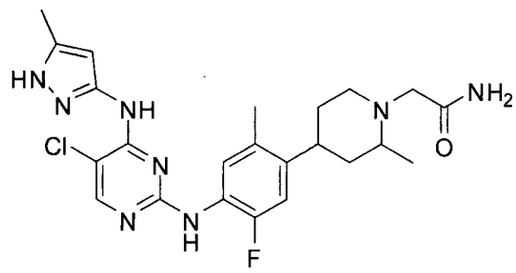
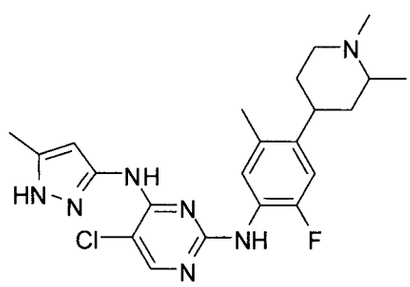
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(3-isopropil-1,2,4-oxadiazol-5-il)-metanona	ESMS *m/z* 554.2 ($M + H^+$); ^1H RMN (400 MHz, $CDCl_3$) δ 9.67 (br s, 2H), 8.50 (s, 1H), 8.07 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 12.4 Hz, 1H), 6.16 (s, 1H), 5.53 (s, 1H), 3.98 (d, *J* = 13.2 Hz, 1H), 3.34 (dt, *J* = 2.0, 2.8 Hz, 1H), 3.15 (m, 1H), 2.82 (m, 2H), 2.62 (t, *J* = 4.8 Hz, 2H), 2.34 (s, 3H),	0.091

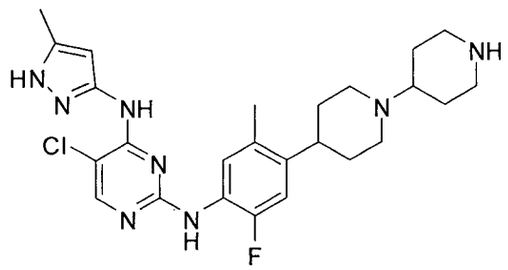
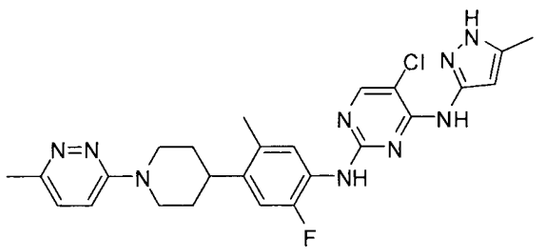
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
		2.25 9s, 3H), 1.90 (m, 2H), 1.76 (2 H)	
	 N2-(4-(1-((5-terbutil-1,2,4-oxadiazol-3-il)-metil)-piperidin-4-il)-2,5-dimetil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 550.3 ($M + H^+$)	0.025
	 N2-(4-(1-((5-terbutil-1,2,4-oxadiazol-3-il)-metil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-	ESMS *m/z* 554.3 ($M + H^+$)	0.077

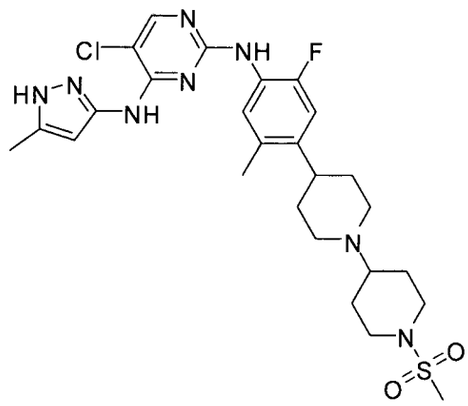
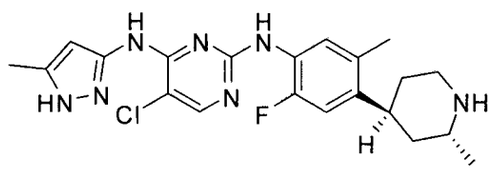
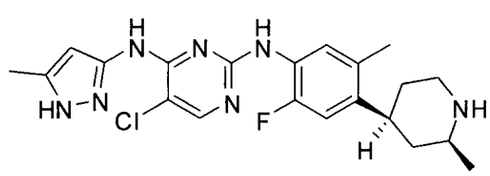
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	pirimidin-2,4-diamina		
	 5-cloro-N4-(5-etil-1H-pirazol-3-il)-N2-(4-(1-etil-piperidin-4-il)-2-fluoro-5-metil-fenil)-pirimidin-2,4-diamina	ESMS *m/z* 458.2 ($M + H^+$)	0.022
	 5-cloro-N2-(4-(1-(2-(3-isopropil-1,2,4-oxadiazol-5-il)-etil)-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 550.3 ($M + H^+$)	0.039

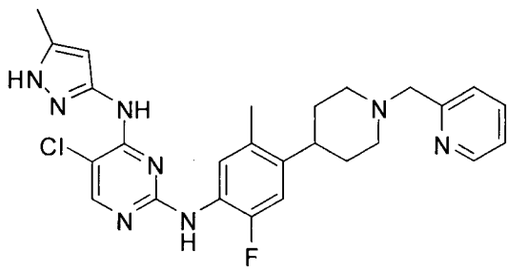
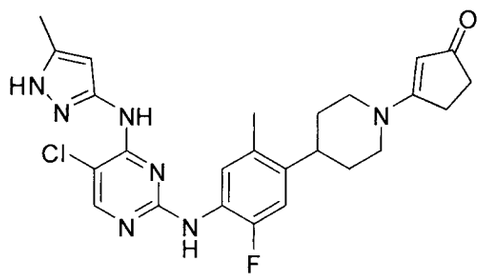
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(3-isopropil-1,2,4-oxadiazol-5-il)-metanona	ESMS *m/z* 550.2 ($M + H^+$)	0.018
	 5-cloro-N4-(5-etil-1H-pirazol-3-il)-N2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil)-pirimidin-2,4-diamina	ESMS *m/z* 444.2 ($M + H^+$)	0.013

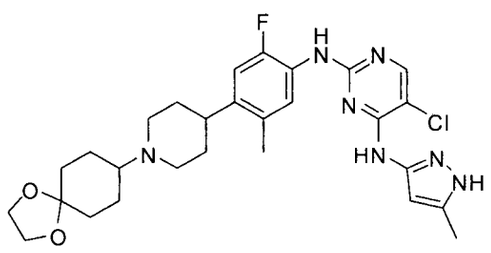
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(4-(1-ciclobutil-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 470.2 ($M + H^+$)	0.050
	 5-cloro-N2-(2-fluoro-5-metil-4-(2-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 430.2 ($M + H^+$)	0.018

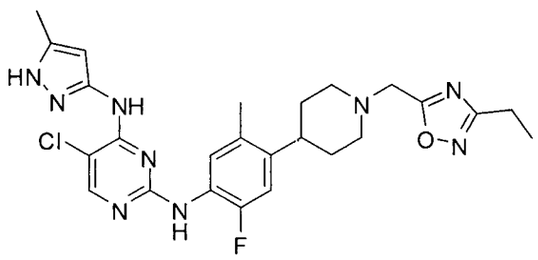
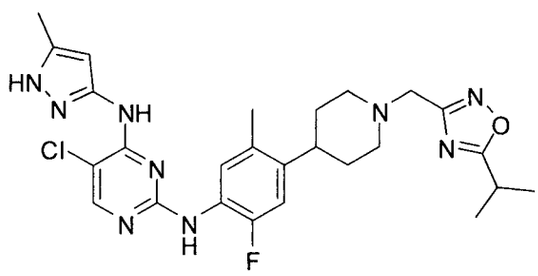
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-2-metil-piperidin-1-il)-acetamida	ESMS *m/z* 487.2 ($M + H^+$)	0.006
	 5-cloro-N2-(4-(1,2-dimetil-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 444.2 ($M + H^+$)	0.009

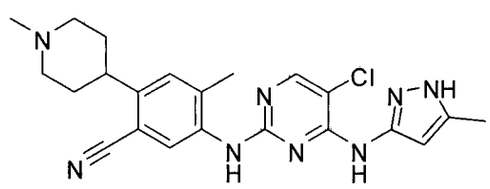
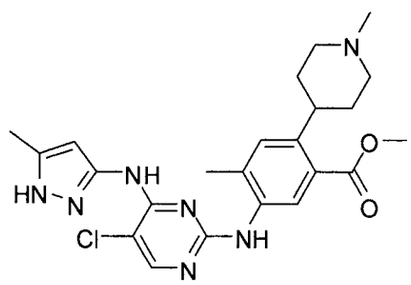
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 N2-(4-(1,4'-bipiperidin-4-il)-2-fluoro-5-metil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 499.2 ($M + H^+$)	0.437
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(6-metil-piridazin-3-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 508.2 ($M + H^+$)	0.097

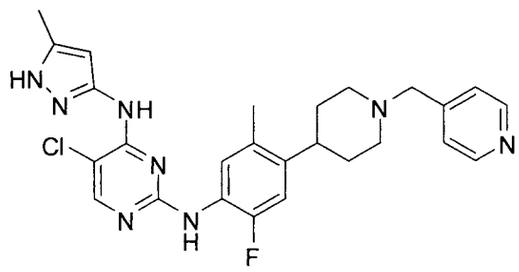
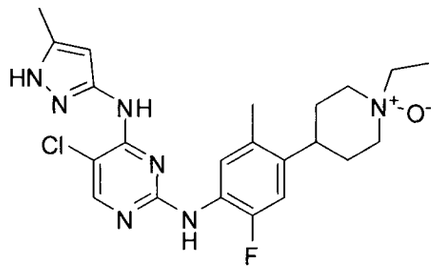
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(2-fluoro-5-metil-4-(1'-(metil-sulfonil)-1,4'-bipiperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 577.2 ($M + H^+$)	0.009
	 5-cloro-N2-(2-fluoro-5-metil-4-((trans)-2-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 430.2 ($M + H^+$)	0.064
		ESMS *m/z* 430.2 ($M + H^+$)	0.163

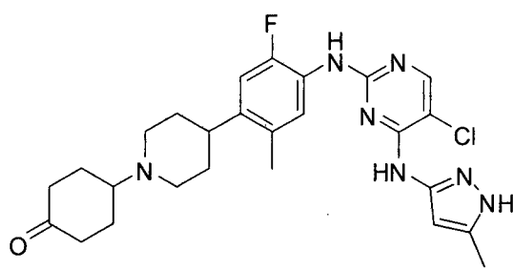
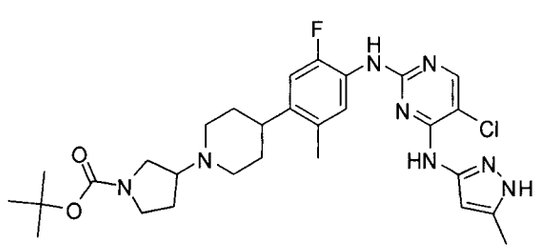
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	5-cloro-N2-(2-fluoro-5-metil-4-((cis)-2-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina		
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(piridin-2-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 507.2 ($M + H^+$)	0.087
	 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-	ESMS *m/z* 496.2 ($M + H^+$); ^{1}H RMN (400 MHz, DMSO-d_6) δ 9.97 (br s, 1H), 9.83 (br s, 1H), 8.90 (s, 1H), 8.32 (d, *J* =	0.048

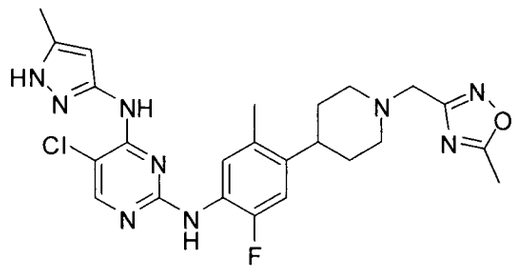
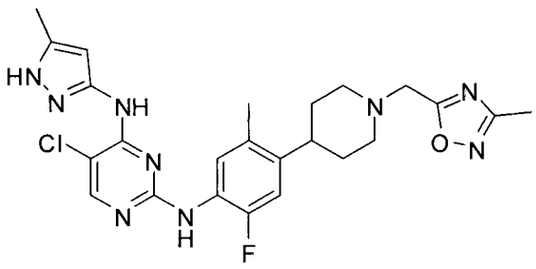
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	piperidin-1-il)-ciclopent-2-enona	6.8 Hz, 1H), 7.88 (d, *J* = 12.8 Hz, 1H), 6.97 (s, 1H), 6.04 (s, 1H), 5.30 (br s, 1H), 4.71 (d, J = 12.0 Hz, 2H), 4.04 (t, *J* = 12.4 Hz, 2H), 3.84 (m, 1H), 3.53 (m, 2H), 3.13 (m, 2H), 3.08 (s, 3H), 2.96 (s, 3H), 2.59-2.40 (m, 4H)	
	 N2-(4-(1-(1,4-dioxaespiro-[4.5]-	ESMS *m/z* 556.3 ($M + H^+$)	0.016

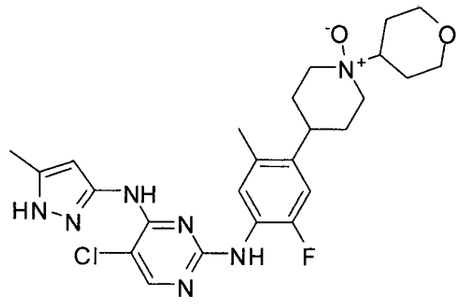
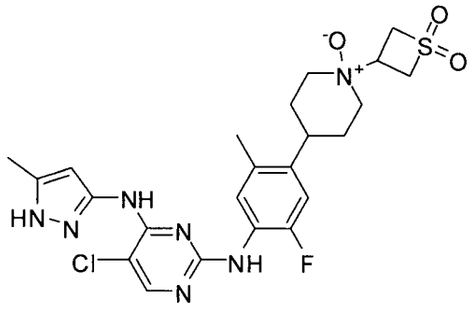
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	decan-8-il)-piperidin-4-il)-2-fluoro-5-metil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina		
	 5-cloro-N2-(4-(1-((3-etil-1,2,4-oxadiazol-5-il)-metil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 526.2 ($M + H^+$)	0.033
	 5-cloro-N2-(2-fluoro-4-(1-((5-isopropil-1,2,4-oxadiazol-3-il)-metil)-piperidin-4-il)-5-metil-fenil)-	ESMS *m/z* 540.2 ($M + H^+$)	0.068

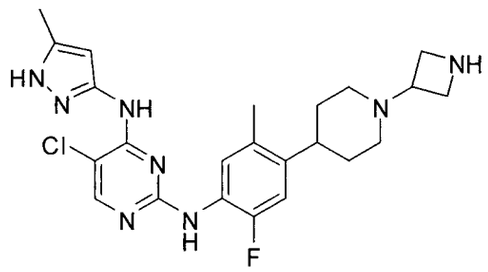
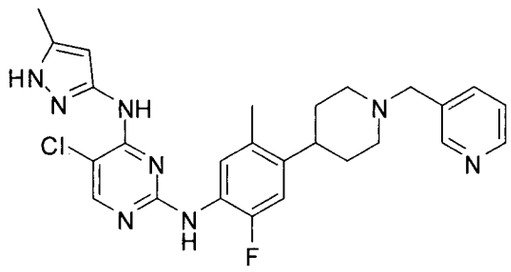
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina		
	 5-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-4-metil-2-(1-metil-piperidin-4-il)-benzonitrilo	ESMS *m/z* 437.2 ($M + H^+$)	0.037
	 5-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-4-metil-2-(1-metil-piperidin-4-il)-benzoato de metilo	ESMS *m/z* 470.2 ($M + H^+$)	0.027

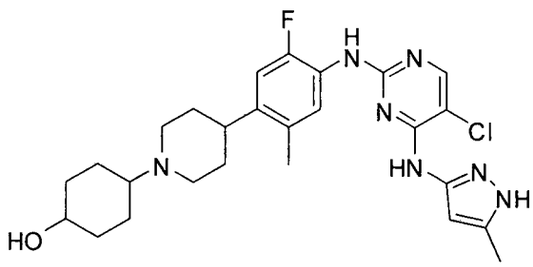
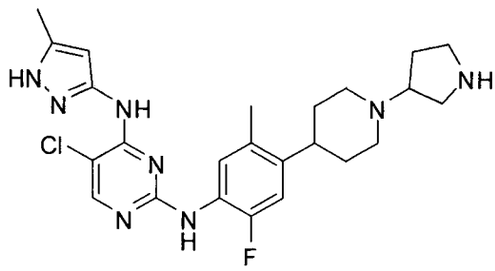
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(piridin-4-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 507.2 ($M + H^+$)	0.093
	 1-óxido de 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-1-etil-piperidina	ESMS *m/z* 460.2 ($M + H^+$); ^{1}H RMN (MeOD-d_4) δ 7.91 (s, 1H), 7.69 (d, 1H), 7.00 (d, 1H), 6.15 (s, 1H), 3.28 (m, 4H), 2.91 (m, 1H), 2.32 (m, 2H), 2.20 (s, 3H), 2.16 (s,	0.37

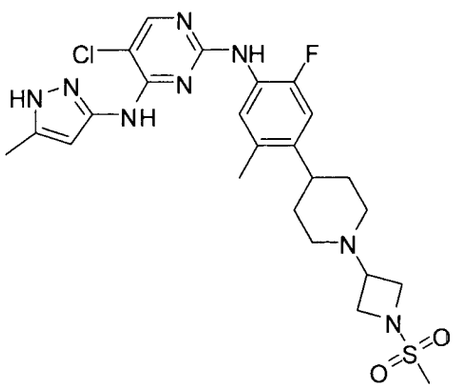
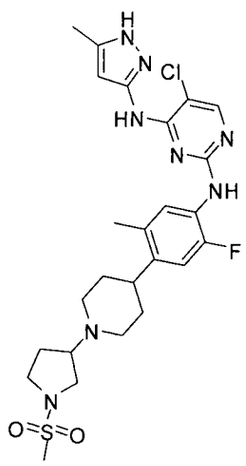
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
		3H), 1.83 (s, 2H), 1.64 (d, 2H), 1.31 (t, 3H).	
	 4-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-ciclohexanona	ESMS *m/z* 512.2 ($M + H^+$)	0.023
	 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-pirrolidin-1-	ESMS *m/z* 585.3 ($M + H^+$)	0.067

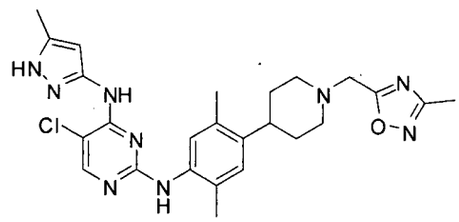
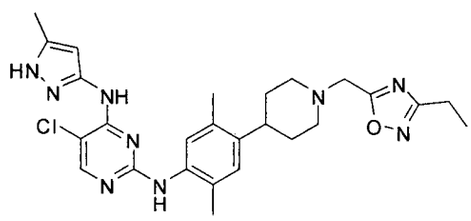
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	carboxilato de terbutilo		
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-((5-metil-1,2,4-oxadiazol-3-il)-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 512.2 ($M + H^+$)	0.023
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-((3-metil-1,2,4-oxadiazol-5-il)-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 512.2 ($M + H^+$)	0.026

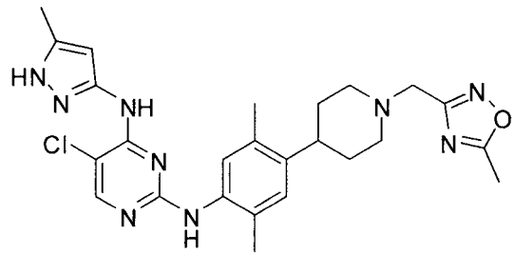
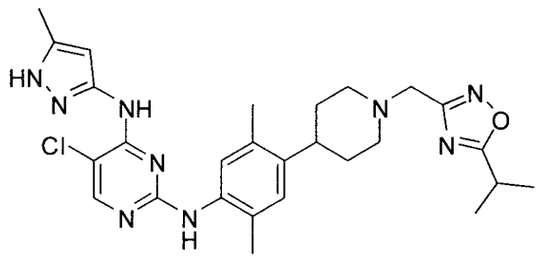
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 1-óxido de 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-1-(tetrahidro-2H-piran-4-il)-piperidina	ESMS *m/z* 516.2 ($M + H^+$)	0.064
	 5-cloro-N2-{4-[1-(1,1-dioxo-1λ6-tietan-3-il)-1-óxido-piperidin-4-il]-2-fluoro-5-metil-fenil}-N4-(5-etil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 536.2 ($M + H^+$)	0.039

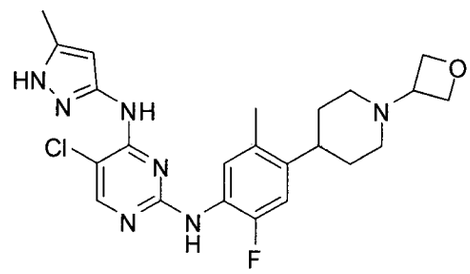
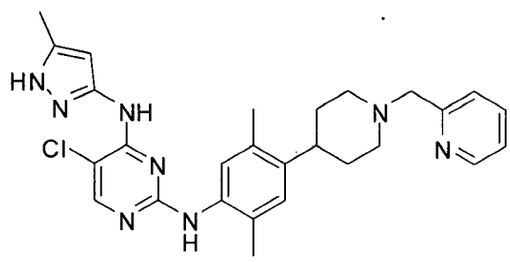
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 N2-(4-(1-(azetidin-3-il)-piperidin-4-il)-2-fluoro-5-metil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 471.2 ($M + H^+$)	0.101
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(piridin-3-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 507.2 ($M + H^+$)	0.079

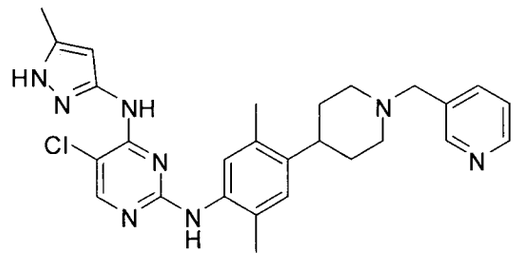
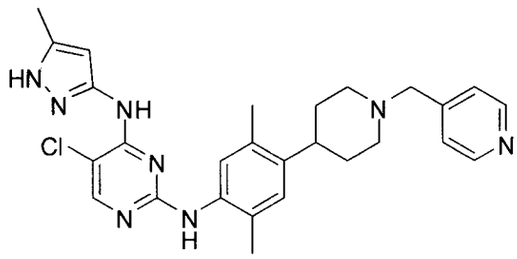
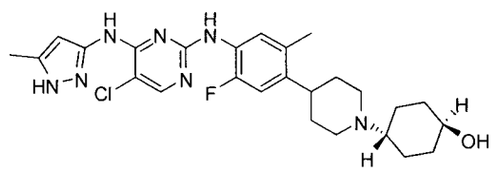
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 4-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-ciclohexanol	ESMS *m/z* 514.2 ($M + H^+$)	0.026
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(pirrolidin-3-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 485.2 ($M + H^+$)	0.101

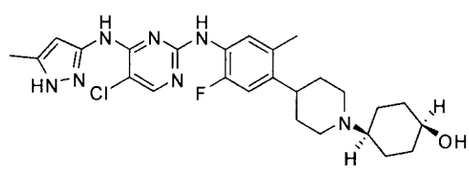
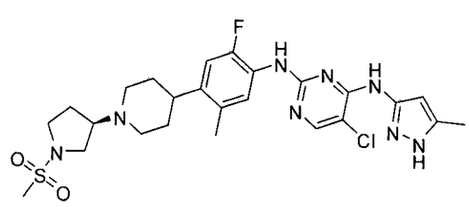
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(1-(metil-sulfonil)-azetidin-3-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 549.2 ($M + H^+$)	0.032
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(1-(metil-sulfonil)-pirrolidin-3-il)-	ESMS *m/z* 563.2 ($M + H^+$)	0.038

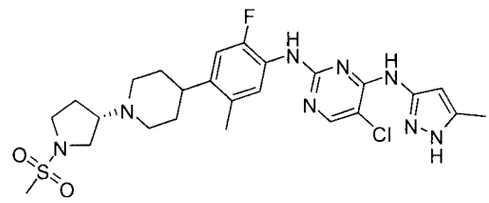
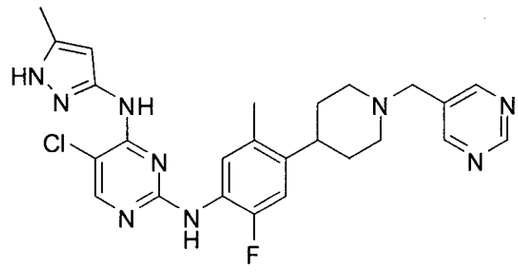
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina		
	 5-cloro-N2-(2,5-dimetil-4-(1-((3-metil-1,2,4-oxadiazol-5-il)-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 508.2 ($M + H^+$)	0.006
	 5-cloro-N2-(4-(1-((3-etil-1,2,4-oxadiazol-5-il)-metil)-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 522.2 ($M + H^+$)	0.006

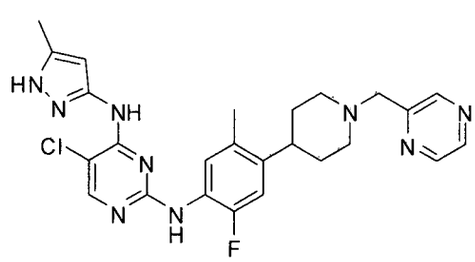
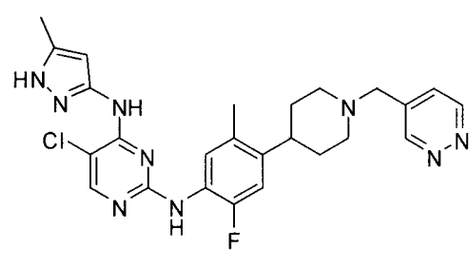
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(2,5-dimetil-4-(1-((5-metil-1,2,4-oxadiazol-3-il)-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 508.2 ($M + H^+$)	0.005
	 5-cloro-N2-(4-(1-((5-isopropil-1,2,4-oxadiazol-3-il)-metil)-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 536.3 ($M + H^+$)	0.025

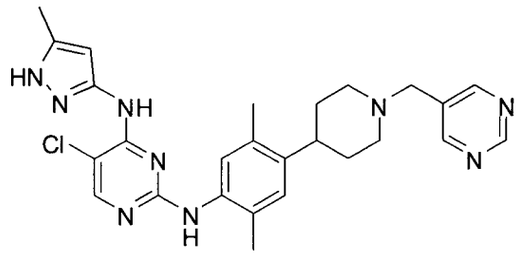
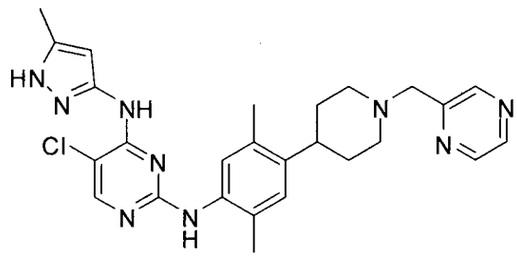
	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(oxetan-3-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 472.2 ($M + H^+$)	0.015
	 5-cloro-N2-(2,5-dimetil-4-(1-(piridin-2-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 503.2 ($M + H^+$)	0.007

	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 5-cloro-N2-(2,5-dimetil-4-(1-(piridin-3-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 503.2 ($M + H^+$)	0.006
	 5-cloro-N2-(2,5-dimetil-4-(1-(piridin-4-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 503.2 ($M + H^+$)	0.008
	 Trans-4-(4-(4-(5-cloro-4-(5-metil-	ESMS *m/z* 514.2 ($M + H^+$)	0.027

	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-ciclohexanol		
	 Cis-4-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-ciclohexanol	ESMS *m/z* 514.2 ($M + H^+$)	0.021
	 (R)-5-cloro-N2-(2-fluoro-5-metil-4-(1-(1-(metil-sulfonil)-pirrolidin-3-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS m/z 563.2 (M + H+)	0.025

	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	 (S)-5-cloro-N2-(2-fluoro-5-metil-4-(1-(1-(metil-sulfonil)-pirrolidin-3-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 563.2 ($M + H^+$)	0.030
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(pirimidin-5-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 508.2 ($M + H^+$); ^{1}H RMN (400 MHz, CD_3OD) δ 9.09 (s, 1H), 8.81 (s, 2H), 8.00 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 13.2 Hz, 1H), 6.23 (br s, 1H), 3.65 (s,	0.037

	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
		2H), 3.03 (m, 2H), 2.76 (m, 1H), 2.27 (s, 3H), 2.25 (s, 3H), 2.25 (m, 2H), 1.80-1.68 (m, 4H)	
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(pirazin-2-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 508.2 ($M + H^+$)	0.036
	 5-cloro-N2-(2-fluoro-5-metil-4-(1-	ESMS *m/z* 508.2 ($M + H^+$)	0.027

	ESTRUCTURA	RMN o ESMS	IGF-1R Ba/F3 IC_{50} (μM)
	(piridazin-4-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina		
	 5-cloro-N2-(2,5-dimetil-4-(1-(pirimidin-5-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 504.2 ($M + H^+$)	0.004
	 5-cloro-N2-(2,5-dimetil-4-(1-(pirazin-2-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	ESMS *m/z* 504.2 ($M + H^+$)	0.010

Ensayos

La IC_{50} de un fármaco se puede determinar construyendo una cuerva de respuesta a la dosis, y examinando el efecto de diferentes concentraciones del antagonista sobre la reversión de la actividad del agonista. Se pueden calcular los valores IC_{50} para un antagonista dado mediante la determinación de la concentración necesaria para inhibir la mitad de la máxima respuesta biológica del agonista. Para calcular los valores IC_{50}, se genera una serie de datos de respuesta a la dosis (por ejemplo, concentraciones de fármaco x1, x2, ..., xn, e inhibiciones del crecimiento y1, y2, ..., yn, en donde los valores de **y** están en el intervalo de 0 a 1). Los valores IC_{50} se pueden determinar mediante un sistema auxiliado por computadora, utilizando la fórmula:

$$y = D+((A-D)/(1+10^{(x-\log(IC50)B)})$$

en donde A es la proporción de inhibición del crecimiento entre la concentración más baja de fármaco y el control; B es la inclinación de la curva sigmoidal; y D es la proporción de inhibición del crecimiento entre la concentración más alta de fármaco y el control.

El valor IC_{50} se da como la concentración del compuesto de prueba que da como resultado una inhibición del crecimiento que es el 50 por ciento más baja que la obtenida utilizando el control sin inhibidor. Los compuestos de la invención en forma libre o en forma de sal farmacéuticamente aceptable pueden exhibir valiosas propiedades farmacológicas, por ejemplo, como se indica por las pruebas *in vitro* descritas en esta solicitud. En general, los

compuestos de la invención tienen valores IC_{50} desde 1nM hasta 10μM. En algunos ejemplos, los compuestos de la invención tienen valores IC_{50} desde 0.01 μM hasta 5 μM. En otros ejemplos, los compuestos de la invención tienen valores IC_{50} desde 0.01 μM hasta 1 μM, o más en particular desde 1 nM hasta 1 μM. En todavía otros ejemplos, los compuestos de la invención tienen valores IC_{50} de menos de 1 nM o más de 10 μM. Los compuestos de la invención pueden exhibir un porcentaje de inhibición mayor del 50 por ciento, o en otras modalidades, pueden exhibir un porcentaje de inhibición mayor de aproximadamente el 70 por ciento, contra IGF-1R a 10 μM.

Panel de la línea celular Ba/F3 y reactivos

Ba/F3 es una línea celular de linfoma pro-B dependiente de IL-3 de murino. Se utilizan las células Ba/F3 progenitoras para generar un panel de sub-líneas cuya proliferación y sobrevivencia se hace independiente de IL-3 mediante la transducción estable con cinasas de tirosina individuales activadas mediante la fusión con la porción amino-terminal de TEL (aminoácidos 1-375) o BCR. Con el objeto de generar las líneas celulares Ba/F3 transformadas por las fusiones de Tel-Cinasa de Tirosina (TK), las células Ba/F3 progenitoras se infectan con a retrovirus que aloja cada cinasa de fusión de TEL, y se someten a selección con puromicina y retiro de IL-3, para obtener las células Ba/F3 transformadas, independientes de IL-3.

Cada una de las células Ba/F3 transformadas se cultiva en un medio RPMI-1640 (Gibco Cat #11875093, Carlsbad, CA) complementado con suero bovino fetal al 10 por ciento (Hyclone Cat

#SV30014.03, Logan, UT), 4.5 gramos/litro de glucosa (Sigma #G5400, St. Louis, MO), 1.5 gramos/litro de bicarbonato de sodio (Biowhittaker #17-613E, Walkersville, MD), y penicilina/ estreptavidina (Pen/Strep) (Gibco #10378-016, Carlsbad, CA). Las células se dividen dos veces por semana.

Ensayo de inhibición de viabilidad de células Ba/F3

Se determina la potencia de los compuestos de prueba contra diferentes líneas Ba/F3 transformadas por Tel-TK como sigue. Las células BaF3 Tel-TK que crecen exponencialmente se diluyen en el medio fresco hasta 75,000 células/mililitro, y se siembran en placas de 384 pozos (3,750 células/pozo) a 50 microlitros/pozo, utilizando un dosificador de líquidos µFill (BioTek, Winooski, VT, EUA). Se ejecutan placas duplicadas por cada línea celular. Los compuestos de prueba y de control se diluyen en serie con sulfóxido de dimetilo, y se arreglan en una placa de polipropileno de 384 pozos. Se transfieren 50 nanolitros del compuesto a las placas de ensayo utilizando un dispositivo de transferencia de picos, y las placas se incuban a 37°C (con CO_2 al 5 por ciento) durante 48 horas. Se agregan 25 microlitros de Britelite (Perkin Elmer), y se cuantifica la luminiscencia utilizando el Analyst GT (Molecular Devices). Se utiliza el software de ajuste de la curva de costumbre para producir un ajuste logístico del porcentaje de viabilidad celular como una función del logaritmo de la concentración del inhibidor. La IC_{50} se interpola como la concentración del compuesto necesaria para reducir la viabilidad celular hasta el 50 por ciento de un control de sulfóxido de

dimetilo. Las células Ba/F3 progenitoras que se mantienen y se cultivan en la presencia de IL-3 (1 nanogramo/mililitro al final) se diluyen en el medio fresco que contiene IL-3 (1 nanogramo/mililitro al final) hasta 75,000 células/ mililitro siguiendo el mismo procedimiento como se describe anteriormente.

Ensayo Enzimático HTRF

IGF-1R e INSR (receptor de insulina) se adquieren en Upstate. Los siguientes reactivos se preparan internamente; regulador de cinasa 10 x (KB) (Tris 200 mM (pH de 7.0), $MgCl_2$ 100 mM, $MnCl_2$ 30 mM, $NaVO_4$ 50 nM), ATP 10 mM, 100 miligramos/mililitro de albúmina de suero bovino, EDTA 0.5 M, KF 4 M. Se utiliza una Proxiplate-384 de Perkin-Elmer para el establecimiento del ensayo. Todos los reactivos HTRF, incluyendo el sustrato (Biotina-poli-GT (61GT0BLB), Mab PT66-K, (61T66KLB), Estreptavidina-XL^{ent} (611SAXLB)) se adquieren en CIS-US, Inc.

La mezcla de sustrato/ATP se prepara mediante la adición de ATP (concentración final de 3 µM), y poli-GT biotinilada (concentración final de 10 nanogramos/microlitro) en KB 1x, y se dosifica en la Proxiplate-384 a 5 microlitros/pozo, utilizando µFill (Bio-TEK). Los compuestos diluidos en serie (en sulfóxido de dimetilo) se transfieren a la placa utilizando una cabeza de picos de 50 nanolitros. Se agregan 5 microlitros de la mezcla enzimática preparada (enzima (concentración final de 5 nanogramos/microlitro), mezclada con albúmina de suero bovino y DTT en KB 1x), para iniciar la reacción de cinasa, utilizando µFill (Bio-TEK). La placa de

ensayo se incuba a temperatura ambiente durante 2 horas. La mezcla de detección se prepara mediante la adición de tanto el Mab PT66-K como Estreptavidina-XL^{ent} en una solución de KB 0.5x que contiene KF (concentración final de 125 mM), EDTA (concentración final de 50 mM), y albúmina de suero bovino (concentración final de 100 microgramos/mililitro). Al final de la reacción, se agregan 10 microlitros de mezcla de detección, y se incuba durante 30 minutos a temperatura ambiente antes de la medición. La señal HTRF se detecta utilizando el Analyst-GT (Molecular Devices).

Ensayo de inhibición de proliferación celular de cáncer

Para luciferizar la línea celular de cáncer, cada línea celular se transduce mediante retrovirus anfolíticos portadores tanto del gen de luciferasa como del gen resistente a la puromicina cuya expresión es impulsada por LTR. Dicho de una manera breve, el vector retroviral pMSCV-Puro-Luc se transfecta en la línea celular Phoenix utilizando Fugene6 (Roche) de acuerdo con las instrucciones del fabricante. Dos días después de la transfección, Se cosecha el sobrenadante que contiene al virus, y se filtra con un filtro de 0.2 micras. El virus cosechado se utiliza inmediatamente o bien se almacena a -80°C. Para la infección, las células de cáncer cultivadas se cosechan y se aplican ($5x10^5$ células/pozo en 1 mililitro del medio) a una placa de cultivo de tejido de 6 pozos. Para cada pozo, se agregan 3 mililitros de sobrenadante de virus, junto con 400 microlitros de suero bovino fetal, 40 microlitros de HEPES 1 M (pH de 8.0), y 4 microlitros de Polibrene (10 microgramos/mililitro, Specialty Media). La placa se

centrifuga durante 90 minutos a 2,500 revoluciones por minuto para la infección centrífuga, y se transfiere a una incubadora para la infección durante la noche. Al día siguiente, la línea celular infectada se transfiere a un matraz T-75 que contiene el medio fresco, y se incuba durante un día. Dos días después de la infección, se agrega puromicina en una concentración final de 1 microgramo/mililitro, para iniciar la selección. Dentro de 1 a dos semana, se establece la línea celular resistente a la puromicina después de cuando menos dos divisiones subsiguientes, y se conserva como el suministro luciferizado.

Cada línea celular se cosecha mientras está en crecimiento en fase log mediante tripsinización, y se diluye en el medio respectivo hasta la densidad apropiada antes de la aplicación a la placa. Las células se dosifican utilizando µFill (BioTeK) a 50 microlitros/pozo, en placas de fondo transparente y de paredes blancas (Greiner – a la medida para GNF). Las células se colocan entonces en la incubadora a 37°C, suministrando CO_2 al 5 por ciento durante la noche. Los compuestos se transfieren utilizando 50 nanolitros/pozo de tecnología Pintool por medio de Platemate (Matrix). Luego las placas de ensayo se colocan de regreso en la incubadora durante 3 días. Al tercer día en seguida de la transferencia de los compuestos, se agrega BRITELITE® (Perkin Elmer, diluido de acuerdo con la sugerencia del fabricante) a las placas de ensayo, y se leen en el Analyst GT (Molecular Devices) o Envision (Perkin Elmer). Los datos brutos se generan en RLU.

Actividad Tumoral de los Compuestos de Ejemplo

Se volvieron a suspender de 3 a 4 x 10^6 células de neuroblastoma humano SK-N-MC en HBSS, y se mezclaron en Matrigel al 50 por ciento, en donde se inyectaron subcutáneamente (0.05 mililitros/ratón) a los ratones (HsdNpa:atímicos/nu) sin pelo hembras de 10 a 12 semanas de edad. Los tratamientos se iniciaron cuando los volúmenes tumorales promedio eran de aproximadamente 150 a 200 milímetros cúbicos. Los pesos corporales y los volúmenes tumorales se registraron tres veces por semana. Los volúmenes tumorales se midieron con calibres, y se determinaron de acuerdo con la fórmula: longitud x diámetro^2 x $\pi / 6$. En adición a presentar los cambios fraccionarios de los volúmenes tumorales durante los cursos de tratamiento, la actividad anti-tumoral se expresó como T/C% (cambio promedio del volumen tumoral de los animales tratados / cambio promedio del volumen tumoral de los animales de control) × 100. La eficacia de los compuestos de prueba se determinó iniciando una dosificación oral el día 19 después de la inyección de las células en seguida de la selección aleatoria de los ratones, de tal manera que cada grupo tiene un tamaño de tumor promedio similar. Se continuó la dosificación con un programa apropiado durante 7 días, basándose en la condición de salud general de los animales. Todos los compuestos de prueba se formularon en NMP/PEG300 (10:90), y se aplicaron diariamente mediante intubación oral. El vehículo consistió en NMP/PEG300 (10:90). Todos los volúmenes de aplicación fueron de 5 mililitros/

kilogramo. La actividad de los compuestos de ejemplo de la invención sobre el crecimiento tumoral se muestra en las Tablas 2 a 4.

Tabla 2

	Respuesta del Tumor			
Tratamiento	**T/C (%)**	**Regr. (%)**	**Δ Volumen del tumor (mm^3 promedio ± SEM)**	**Veces de cambio promedio en crecimiento tumoral**
NMP/PEG300 (10/90) 5 mL/kg po q8/16h	100	0	334 ± 59	3.1 ± 0.3
Compuesto de Prueba 1 20 mg/kg, q8/16h, po	53	-	231 ± 145	2.1 ± 0.4
Compuesto de Prueba 1 40 mg/kg, q8/16h, po	35	-	107 ± 48*	1.7 ± 0.2*

Tabla 3

	Respuesta del Tumor			
Tratamiento	**T/C (%)**	**Regr. (%)**	**Δ Volumen del tumor (mm^3 promedio ± SEM)**	**Veces de cambio promedio en crecimiento tumoral**
NMP/PEG300 (10/90) 5 mL/kg po q8/16h	100	0	334 ± 59	3.1 ± 0.3
Compuesto de Prueba 2 12.5 mg/kg, q8/16h, po	69	-	232 ± 103	2.5 ± 0.4
Compuesto de Prueba 2 25 mg/kg, q8/16h, po	22	-	42 ± 10*	1.5 ± 0.2*

Tabla 4

	Respuesta del Tumor			
Tratamiento	**T/C (%)**	**Regr. (%)**	**Δ Volumen del tumor (mm^3 promedio ± SEM)**	**Veces de cambio promedio en crecimiento tumoral**
NMP/PEG300 (10/90) 5 mL/kg po q8/16h	100	0	334 ± 59	3.1 ± 0.3
Compuesto de Prueba 3 12.5 mg/kg, q8/16h, po	58	-	220 ± 67	2.2 ± 0.3
Compuesto de Prueba 3 25 mg/kg, q8/16h, po	26	-	102 ± 40*	1.6 ± 0.3*

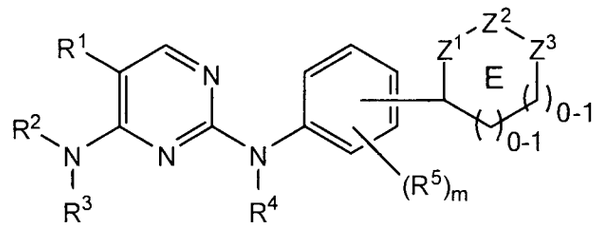
< 0.05 vs. Controles de Vehículo – ANOVA en rangos y prueba de Dunnett *post hoc*.

*****

Se entiende que los Ejemplos y modalidades descritos en la presente son para propósitos ilustrativos solamente, y que serán sugeridas diferentes modificaciones o cambios a la luz de los mismos, para las personas expertas en la técnica, y se deben incluir dentro del espíritu y alcance de esta solicitud y dentro del alcance de las reivindicaciones adjuntas. Todas las publicaciones, patentes, y solicitudes de patente citadas en la presente, se incorporan a la presente por referencia para todos los propósitos.

REIVINDICACIONES

1. Un compuesto de la fórmula (1):



(1)

o una sal fisiológicamente aceptable del mismo;

en donde el anillo E puede contener opcionalmente un doble enlace;

uno de Z^1, Z^2 y Z^3 es NR^6, $N(R^6)^+\text{-}O^-$ o $S(O)_{1\text{-}2}$ y los otros son CR_2;

R^1 es halógeno o un alquilo de 1 a 6 átomos de carbono opcionalmente halogenado;

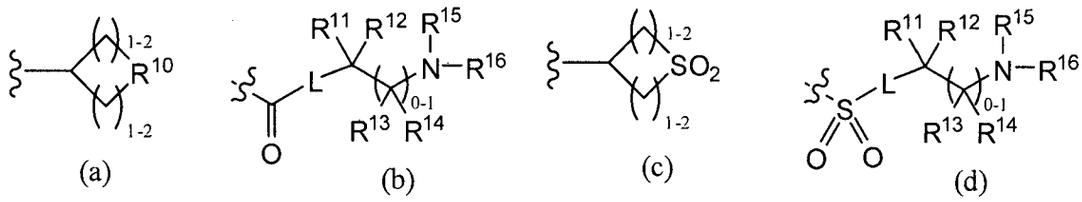
R^2 es piridin-2-onilo, azepan-2-onilo o un heteroarilo monocíclico de 5 a 6 miembros que tiene de 1 a 3 heteroátomos seleccionados a partir de N, O y S; cada uno de los cuales está opcionalmente sustituido con R^9 en donde R^9 es alquilo de 1 a 6 átomos de carbono, halo-alquilo de 1 a 6 átomos de carbono, o cicloalquilo de 3 a 7 átomos de carbono;

R^3 y R^4 son cada uno H;

R^5 es halógeno, hidroxilo, alquilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno, ciano o $C(O)O_{0\text{-}1}R^8$;

R^6 es H; alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con grupos halógeno y/o hidroxilo; $-(CR_2)_p-OR^7$, $-(CR_2)_p-CH(OH)C_tF_{2t+1}$ en donde t es de 1 a 3, $(CR_2)_p-CN$; $(CR_2)_p-NR(R^7)$, $-(CR_2)_p-C(O)OR^7$, $(CR_2)_pNR(CR_2)_pOR^7$, $(CR_2)_pNR-L-C(O)R^8$, $C(O)-(CR_2)_qOR^8$, $-C(O)O-(CR_2)_p-NRR^7$, $-C(O)-(CR_2)_p-OR^7$, L-Y, $-L-C(O)R^7$, $-L-C(O)-NRR^7$, $-L-C(O)-NR-(CR_2)_p-NRR^7$, $-L-C(O)NR(CR_2)_pOR^7$, $-L-C(O)-(CR_2)_q-NR-C(O)-R^8$, $-L-C(O)NR(CR_2)_pSR^7$, $-L-C(O)NR(CR_2)_pS(O)_{1-2}R^8$, $-L-S(O)_2R^8$, $-L-S(O)_2-(CR_2)_q-NRR^7$, $-L-S(O)_2NR(CR_2)_pNR(R^7)$ o $-L-S(O)_2NR(CR_2)_pOR^7$;

de una manera alternativa, R^6 es un radical seleccionado a partir de la fórmula (a), (b), (c) o (d):



(a) (b) (c) (d)

R^{10} es O, S, NR^{17} en donde R^{17} es H, alquilo de 1 a 6 átomos de carbono, SO_2R^{8a} o CO_2R^{8a};

R^{11}, R^{12}, R^{13}, R^{14}, R^{15} y R^{16} se seleccionan independientemente a partir de H; alcoxilo de 1 a 6 átomos de carbono; alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con grupos halógeno, amino, o hidroxilo; o R^{11} y R^{12}, R^{12} y R^{15}, R^{15} y R^{16}, R^{13} y

R^{14}, o R^{13} y R^{15}, junto con los átomos con los que están unidos, pueden formar un anillo de 3 a 7 miembros, saturado, insaturado, o parcialmente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O, y S, y opcionalmente sustituido con oxo y de 1 a 3 grupos R^5;

L es $(CR_2)_{1-4}$ o un enlace;

Y es un anillo carbocíclico de 3 a 7 átomos de carbono, arilo de 6 a 10 átomos de carbono, o un heteroarilo de 5 a 10 miembros o anillo heterocíclico de 4 a 10 miembros, cada uno de los cuales está opcionalmente sustituido con 1 a 3 grupos R^5;

R^7, R^8 y R^{8a} son independientemente alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con halógeno, amino, hidroxilo o ciano; $(CR_2)_qY$ o alcoxilo de 1 a 6 átomos de carbono; o R^7 es H;

cada R es independientemente H o alquilo de 1 a 6 átomos de carbono;

R y R^7 junto con N en cada NRR^7 pueden formar un anillo de 5 a 6 miembros que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O, y S, y opcionalmente sustituido con oxo y de 1 a 3 grupos R^5;

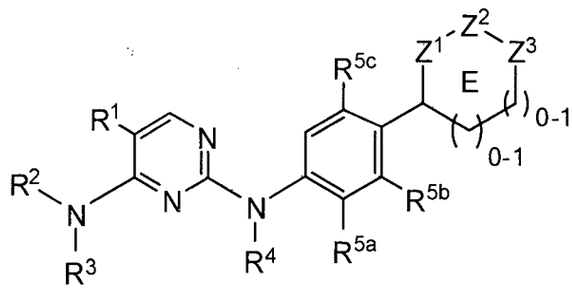
m es de 2 a 4;

n es de 1 a 3;

p es de 1 a 4; y

q es de 0 a 4.

2. El compuesto de la reivindicación 1, en donde el compuesto mencionado es de la fórmula (2):



(2)

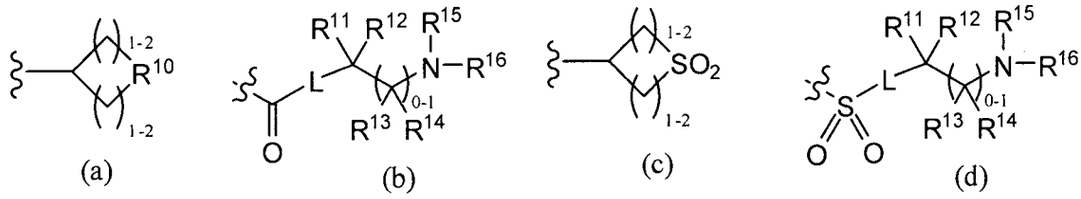
en donde uno de R^{5a}, R^{5b} y R^{5c} es H, y los otros son independientemente halógeno, alquilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, ciano o $C(O)O_{0-1}R^8$ en donde R^8 es alquilo de 1 a 6 átomos de carbono; y

R^1, R^2, R^3, R^4, E, Z^1, Z^2 y Z^3 son como se definen en la reivindicación 1.

3. El compuesto de la reivindicación 2, en donde Z^3 es NR^6 o $N(R^6)^+$-O^-; y Z^1 y Z^2 son CH_2.

4. El compuesto de la reivindicación 3, en donde R^6 es H, alquilo de 1 a 6 átomos de carbono opcionalmente sustituido con grupos halógeno y/o hidroxilo; $-(CR_2)_p-OR^7$, $-(CR_2)_p-CH(OH)C_tF_{2t+1}$ en donde t es de 1 a 3, $(CR_2)_p-CN$; $(CR_2)_p-NR(R^7)$, $-(CR_2)_p-C(O)OR^7$, $C(O)-(CR_2)_qOR^8$, $-C(O)O-(CR_2)_p-NRR^7$, L-Y, $-L-C(O)R^7$, $-L-C(O)-NRR^7$, $-L-C(O)-NR-(CR_2)_p-NRR^7$, $-L-C(O)-(CR_2)_q-NR-C(O)-R^8$, $-L-S(O)_2R^8$, $-L-S(O)_2-(CR_2)_q-NRR^7$,

o un radical seleccionado a partir de la fórmula (a), (b), (c) o (d):



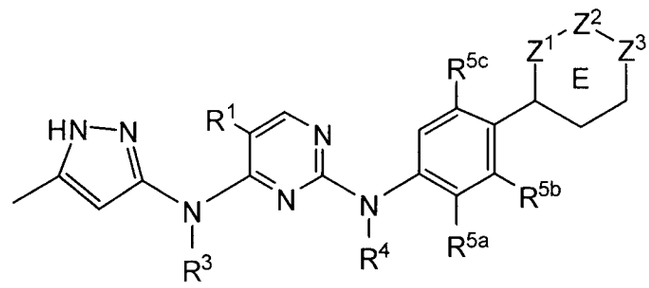
(a) (b) (c) (d)

R^{10} es O, S, NR^{17} en donde R^{17} es H, alquilo de 1 a 6 átomos de carbono, SO_2R^{8a} o CO_2R^{8a} y R^{8a} es alquilo de 1 a 6 átomos de carbono; y

R^7, R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R, L, Y, p y q son como se definen en la reivindicación 1.

5. El compuesto de cualquiera de las reivindicaciones 1 a 4, en donde R^2 es pirazolilo, isoxazolilo, piridin-2-onilo o azepan-2-onilo, cada uno de los cuales está sustituido con alquilo de 1 a 6 átomos de carbono, halo-alquilo de 1 a 6 átomos de carbono, o cicloalquilo de 3 a 7 átomos de carbono.

6. El compuesto de la reivindicación 1, en donde el compuesto mencionado es de la fórmula (3):



(3)

o un tautómero del mismo;

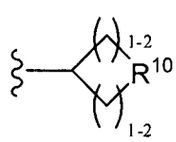
en donde R^{5b} es H; y R^{5a} y R^{5c} son independientemente halógeno, alquilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido

por halógeno, ciano o $C(O)O_{0-1}R^8$ en donde R^8 es alquilo de 1 a 6 átomos de carbono;

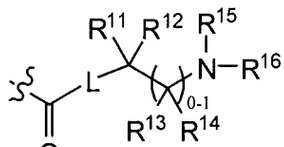
Z^1 y Z^2 son CH^2;

Z^3 es NR^6 o $N(R^6)^+$-O^-;

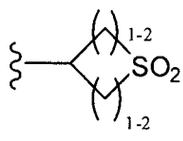
R^6 es H, alquilo de 1 a 6 átomos de carbono opcionalmente sustituido con grupos halógeno y/o hidroxilo; $-(CR_2)_p$-OR^7, $-(CR_2)_p$-$CH(OH)C_tF_{2t+1}$ en donde t es de 1 a 3, $(CR_2)_p$-CN; $(CR_2)_p$-$NR(R^7)$, $-(CR_2)_p$–$C(O)OR^7$, $C(O)$-$(CR_2)_qOR^8$, $-C(O)O$-$(CR_2)_p$-NRR^7, L-Y, -L-$C(O)R^7$, -L–$C(O)$-NRR^7, -L–$C(O)$-NR-$(CR_2)_p$-NRR^7, -L–$C(O)$-$(CR_2)_q$-NR-$C(O)$-R^8, -L-$S(O)_2R^8$, -L-$S(O)_2$-$(CR_2)_q$-NRR^7, o un radical seleccionado a partir de la fórmula (a), (b), (c) o (d):



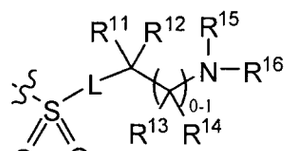
(a)



(b)



(c)



(d)

R^{10} es O, S, NR^{17} en donde R^{17} es H, alquilo de 1 a 6 átomos de carbono, SO_2R^{8a} o CO_2R^{8a} y R^{8a} es alquilo de 1 a 6 átomos de carbono; y

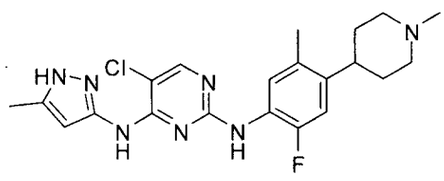
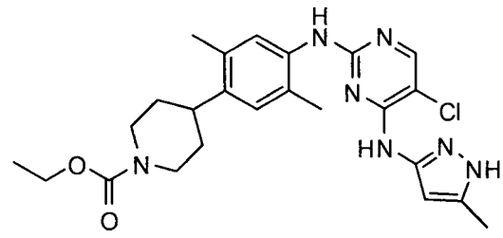
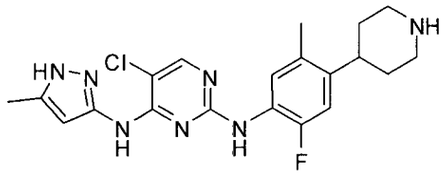
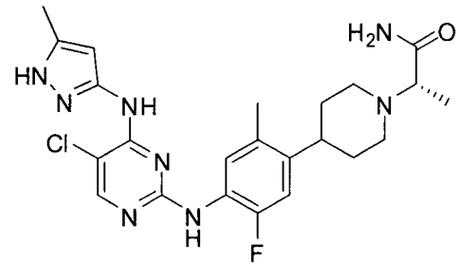
R^1, R^3, R^4, R^7, R^8, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R, L, Y, p, q y E son como se definen en la reivindicación 1.

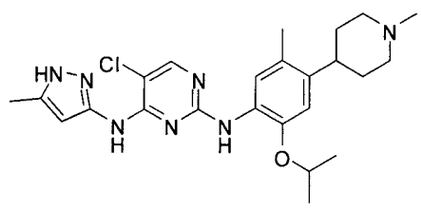
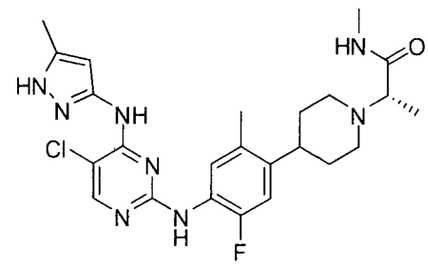
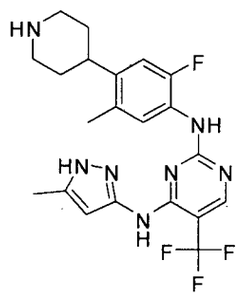
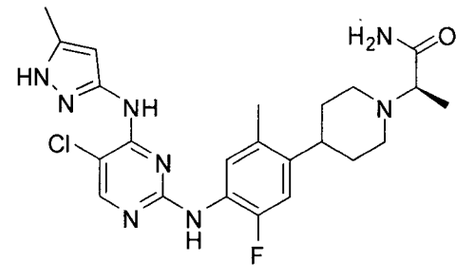
7. El compuesto de la reivindicación 6, en donde R^{5a} es halógeno y R^{5c} es alquilo de 1 a 6 átomos de carbono.

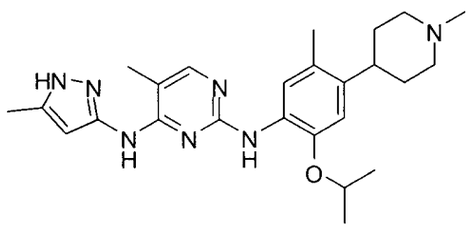
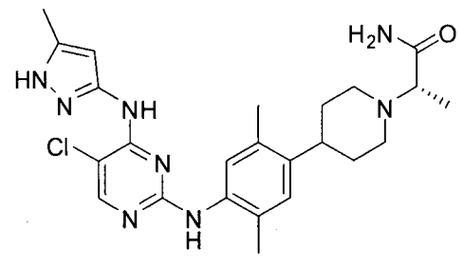
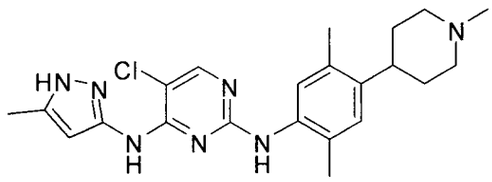
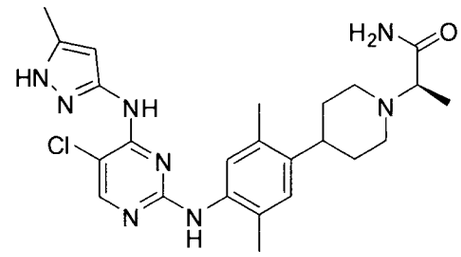
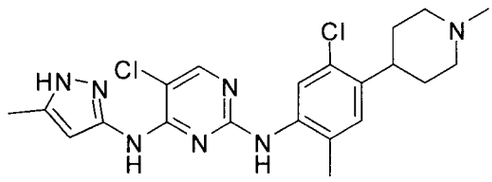
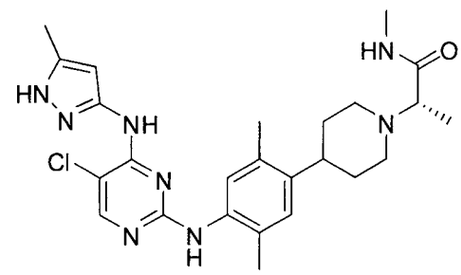
8. El compuesto de la reivindicación 6, en donde R^6 es alquilo de 1 a 6 átomos de carbono, o a un radical de la fórmula (a) o (c); y R^{10} es O.

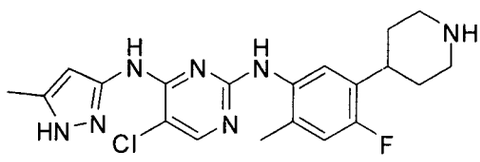
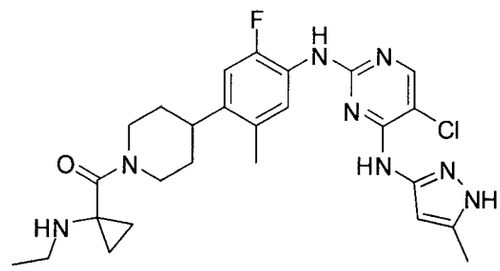
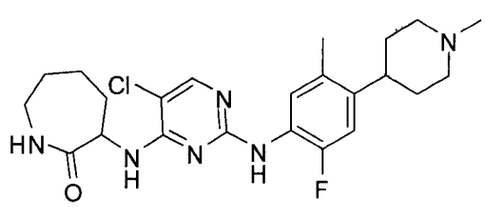
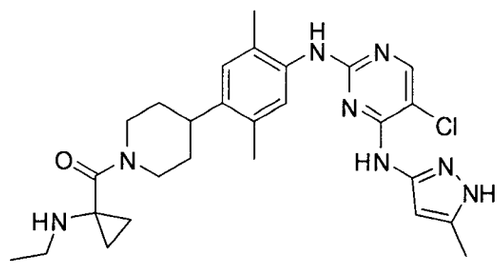
9. El compuesto de cualquiera de las reivindicaciones 1 a 8, en donde R^1 es halógeno.

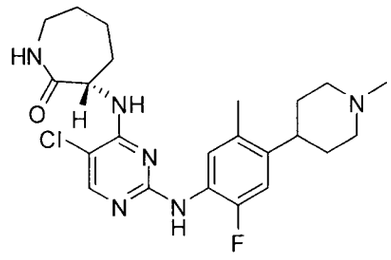
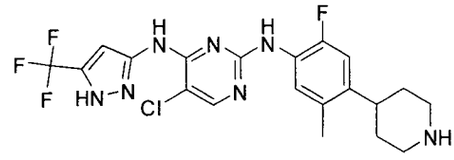
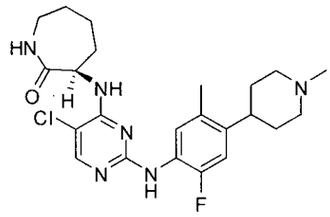
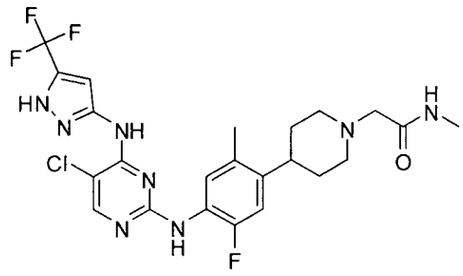
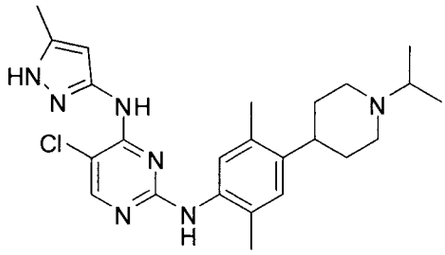
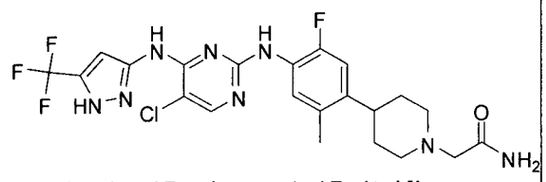
10. El compuesto de la reivindicación 1, en donde el compuesto mencionado se selecciona a partir del grupo:

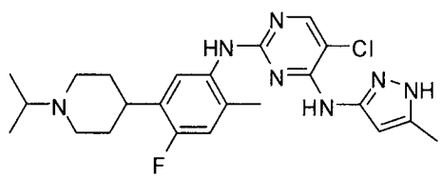
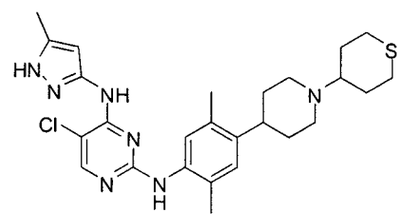
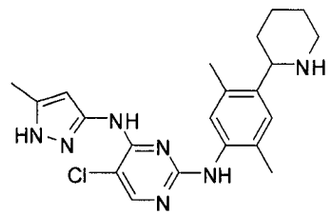
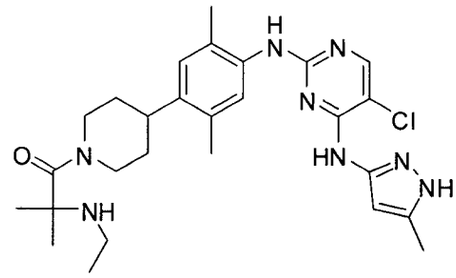
 5-cloro-N2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-carboxilato de etilo
 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 (S)-2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propanamida

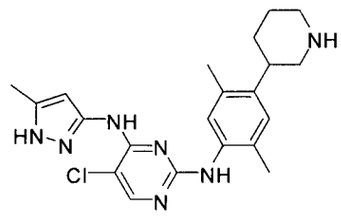
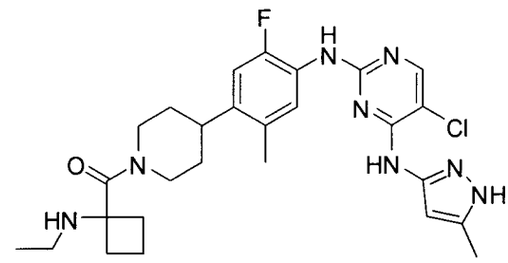
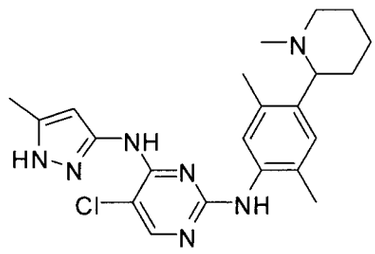
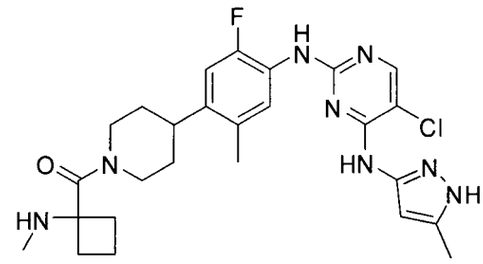
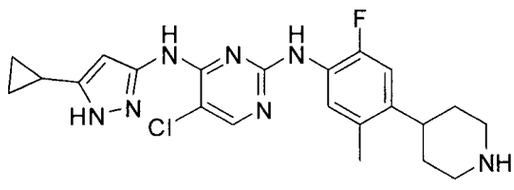
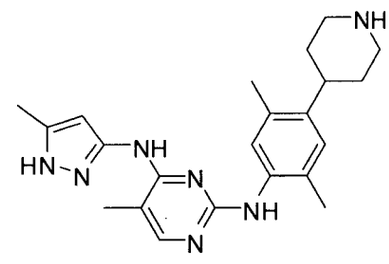
	
5-cloro-N2-(2-isopropoxi-5-metil-4-(1-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	(S)-2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-N-metil-propanamida
	
N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-5-(trifluoro-metil)-pirimidin-2,4-diamina	(R)-2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propanamida

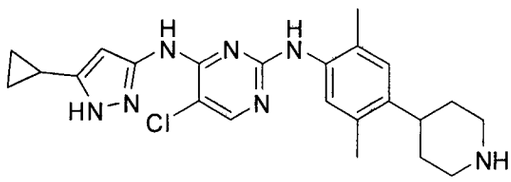
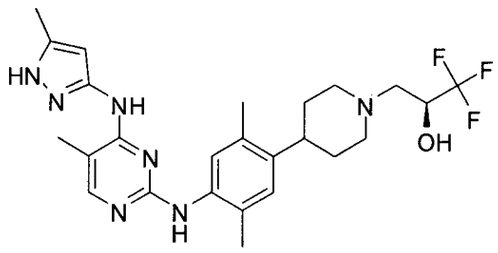
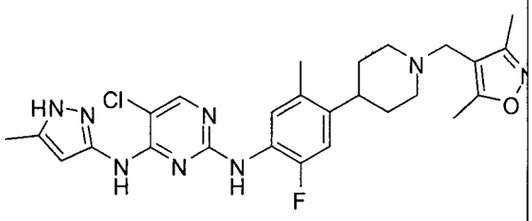
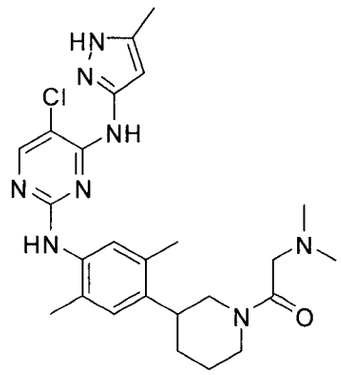
 N2-(2-isopropoxi-5-metil-4-(1-metil-piperidin-4-il)-fenil)-5-metil-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 (S)-2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-propanamida
 5-cloro-N2-(2,5-dimetil-4-(1-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 (R)-2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-propanamida
 5-cloro-N2-(5-cloro-2-metil-4-(1-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-	 (S)-2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-

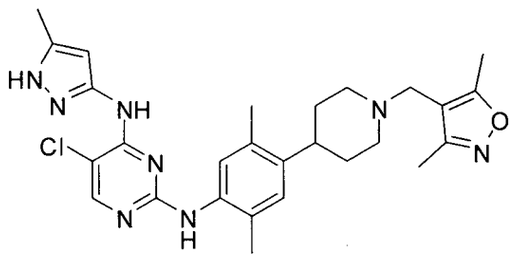
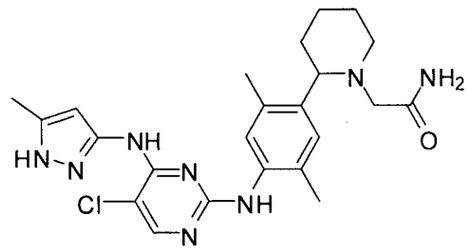
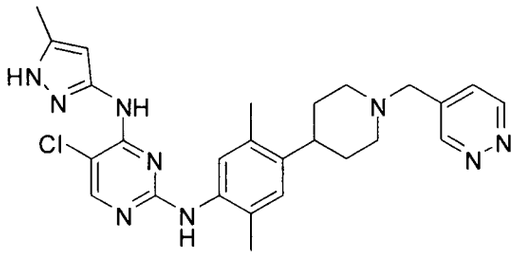
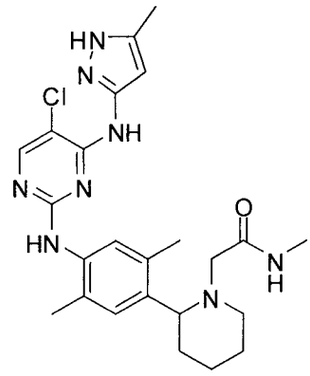
2,4-diamina	2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-propanamida
 5-cloro-N2-(4-fluoro-2-metil-5-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-(etil-amino)-ciclopropil)-metanona
 3-(5-cloro-2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil-amino)-pirimidin-4-il-amino)-azepan-2-ona	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(1-(etil-amino)-ciclopropil)-metanona

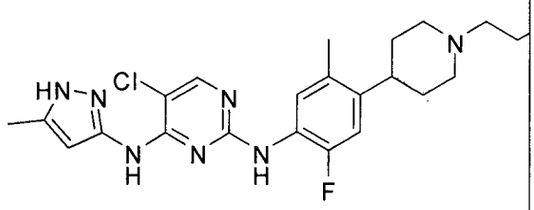
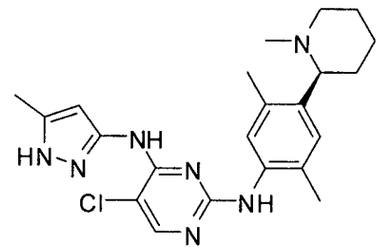
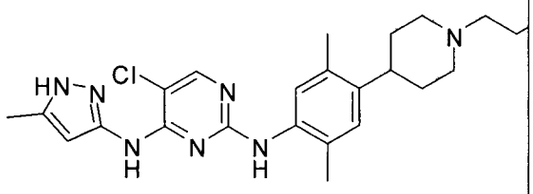
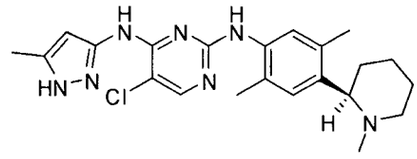
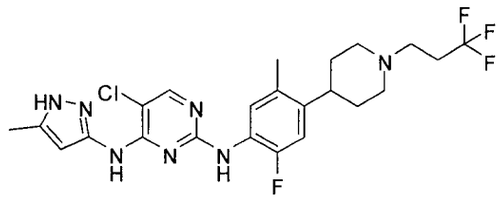
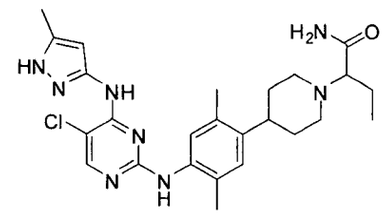
 (S)-3-(5-cloro-2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil-amino)-pirimidin-4-il-amino)-azepan-2-ona	 5-cloro-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-N4-(5-(trifluoro-metil)-1H-pirazol-3-il)-pirimidin-2,4-diamina
 (R)-3-(5-cloro-2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil-amino)-pirimidin-4-il-amino)-azepan-2-ona	 2-(4-(4-(5-cloro-4-(5-(trifluoro-metil)-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-N-metil-acetamida
 5-cloro-N2-(4-(1-isopropil-	 2-(4-(4-(5-cloro-4-(5-(trifluoro-metil)-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-

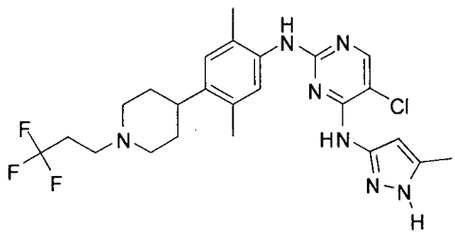
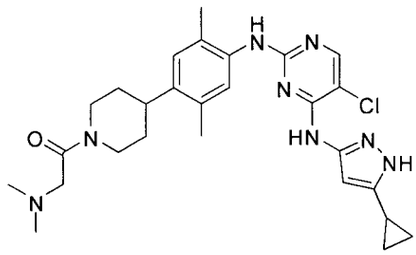
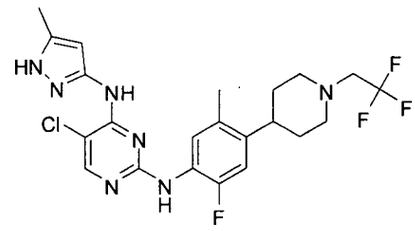
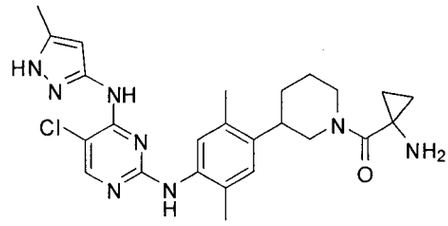
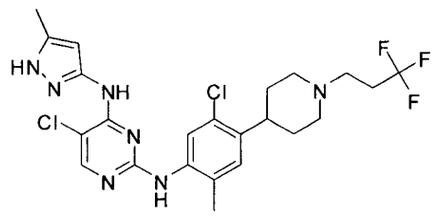
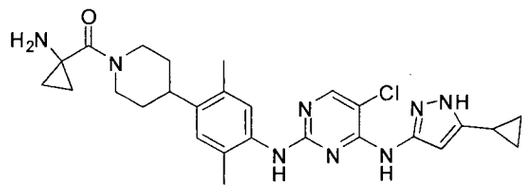
piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	metil-fenil)-piperidin-1-il)-acetamida
 5-cloro-N2-(4-fluoro-5-(1-isopropil-piperidin-4-il)-2-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 5-cloro-N2-(2,5-dimetil-4-(1-(tetrahidro-2H-tiopiran-4-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 5-cloro-N2-(2,5-dimetil-4-(piperidin-2-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(etil-amino)-2-metil-propan-1-ona

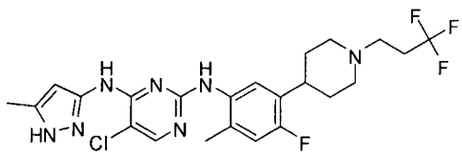
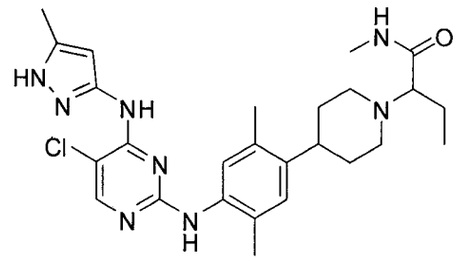
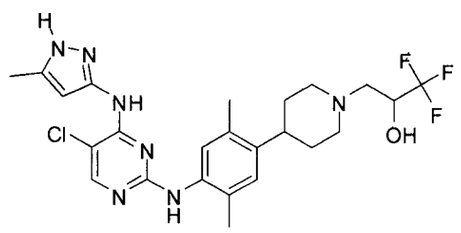
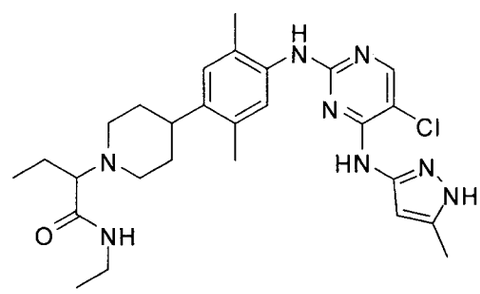
 5-cloro-N2-(2,5-dimetil-4-(piperidin-3-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-(etil-amino)-ciclobutil)-metanona
 5-cloro-N2-(2,5-dimetil-4-(1-metil-piperidin-2-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-(metil-amino)-ciclobutil)-metanona
 5-cloro-N4-(5-ciclopropil-1H-	

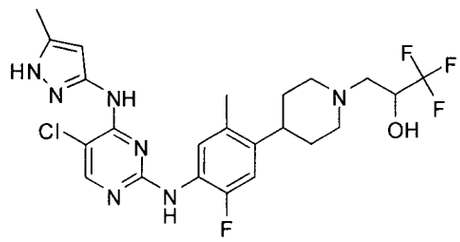
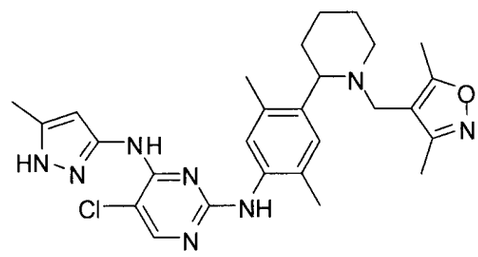
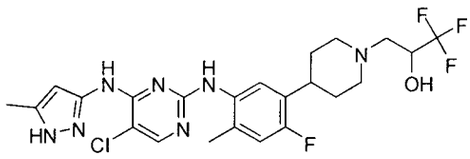
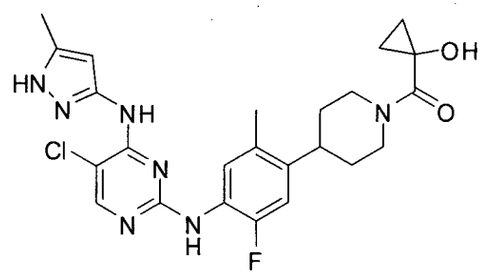
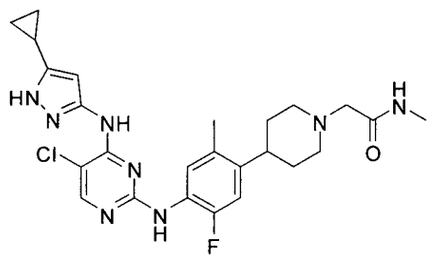
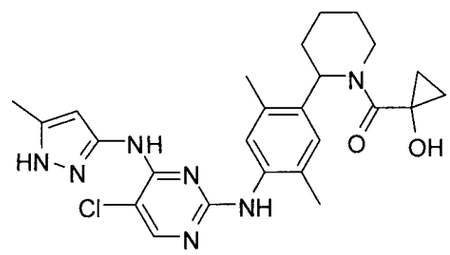
pirazol-3-il)-N2-(2-fluoro-5-metil-4-(piperidin-4-il)-fenil)-pirimidin-2,4-diamina	N2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-5-metil-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 5-cloro-N4-(5-ciclopropil-1H-pirazol-3-il)-N2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-pirimidin-2,4-diamina	 (S)-3-(4-(2,5-dimetil-4-(5-metil-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol
 5-cloro-N2-(4-(1-((3,5-dimetil-isoxazol-4-il)-metil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 1-(3-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(dimetil-amino)-

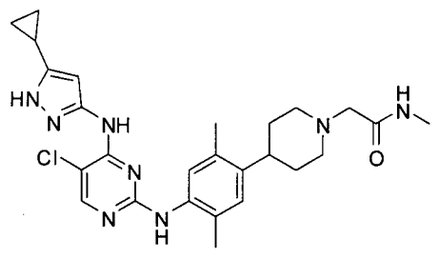
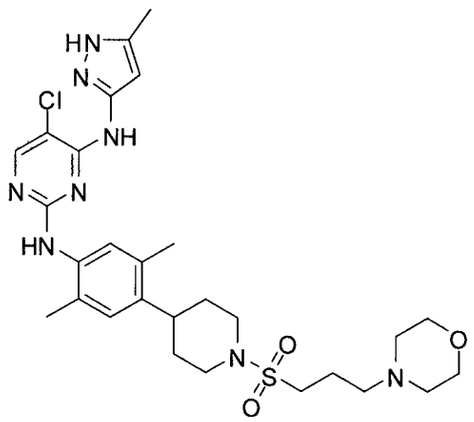
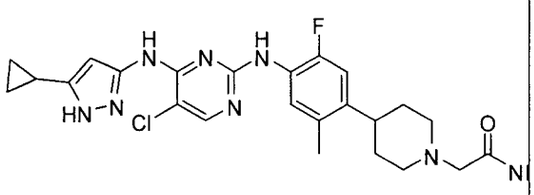
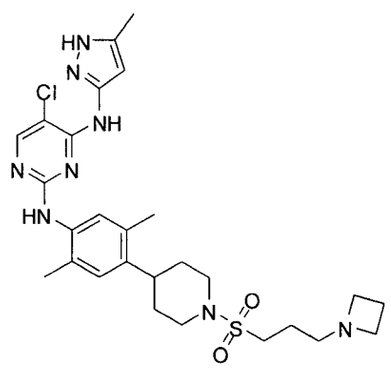
	etanona
 5-cloro-N2-(4-(1-((3,5-dimetil-isoxazol-4-il)-metil)-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 2-(2-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-acetamida
 5-cloro-N2-(2,5-dimetil-4-(1-(piridazin-4-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 2-(2-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida

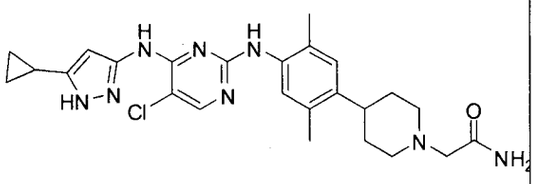
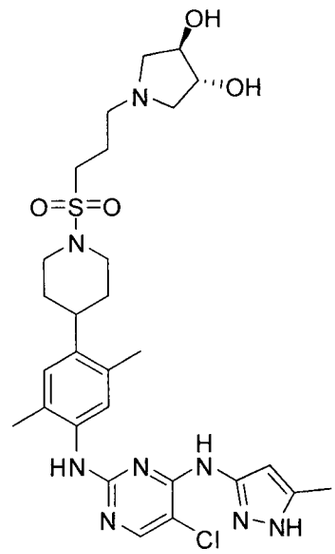
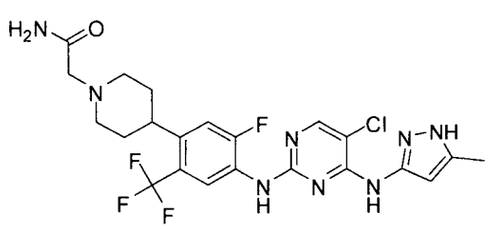
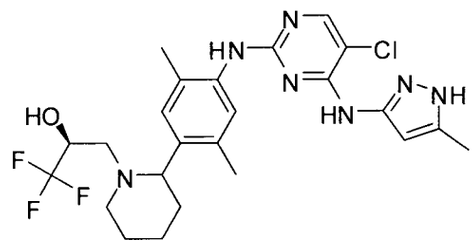
 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-etanol	 (S)-5-cloro-N2-(2,5-dimetil-4-(1-metil-piperidin-2-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-etanol	 (R)-5-cloro-N2-(2,5-dimetil-4-(1-metil-piperidin-2-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 5-cloro-N^2-(2-fluoro-5-metil-4-(1-(3,3,3-trifluoro-propil)-piperidin-4-il)-fenil)- N^4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-

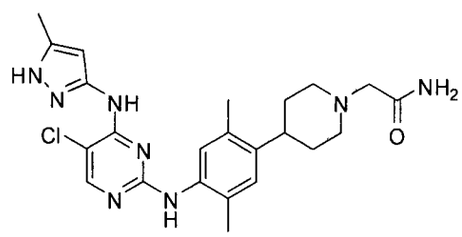
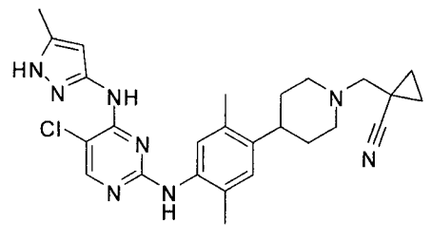
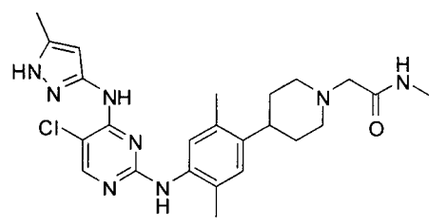
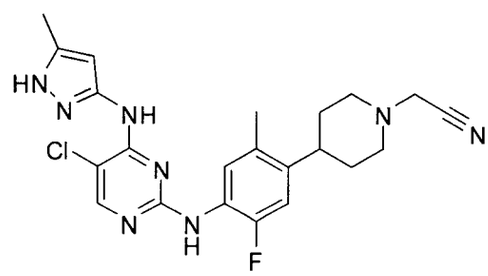
diamina	piperidin-1-il)-butanamida
	
5-cloro-N2-(2,5-dimetil-4-(1-(3,3,3-trifluoro-propil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	1-(4-(4-(5-cloro-4-(5-ciclopropil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona
	
5-cloro-N2-(2-fluoro-5-metil-4-(1-(2,2,2-trifluoro-etil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	(1-amino-ciclopropil)-(3-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-metanona
	

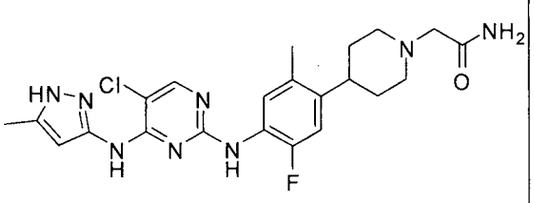
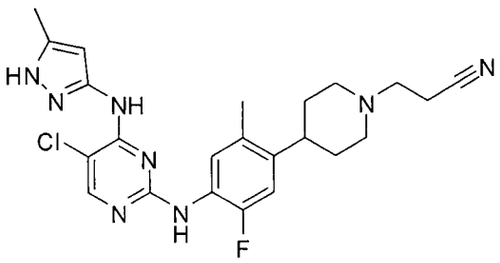
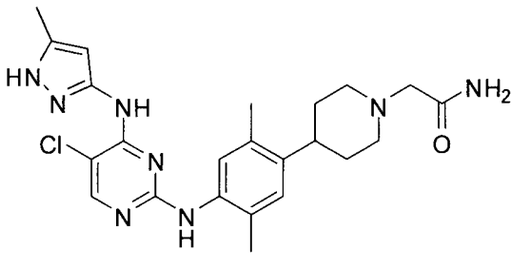
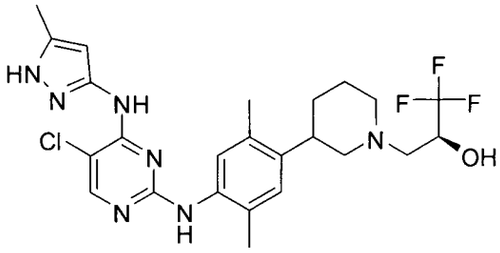
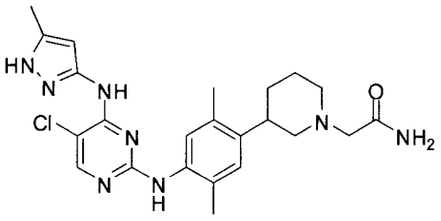
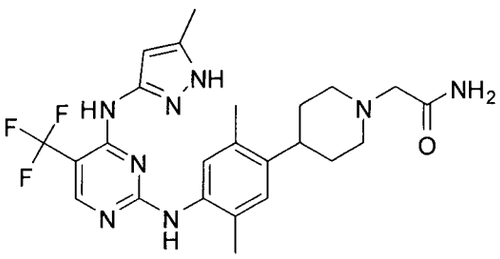
5-cloro-N2-(5-cloro-2-metil-4-(1-(3,3,3-trifluoro-propil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	(1-amino-ciclopropil)-(4-(4-(5-cloro-4-(5-ciclopropil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-metanona
 5-cloro-N2-(4-fluoro-2-metil-5-(1-(3,3,3-trifluoro-propil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-butanamida
 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-etil-butanamida

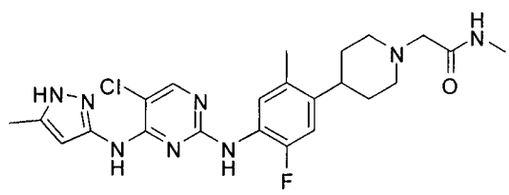
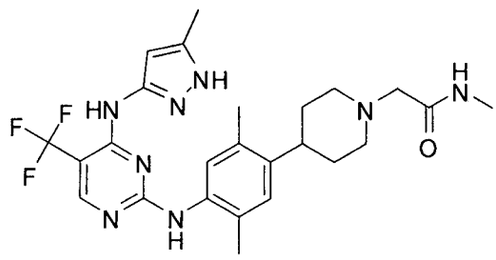
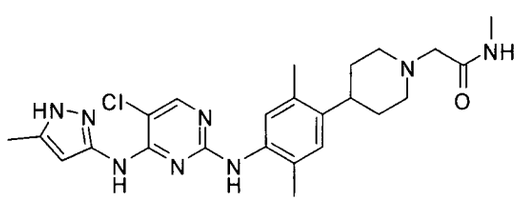
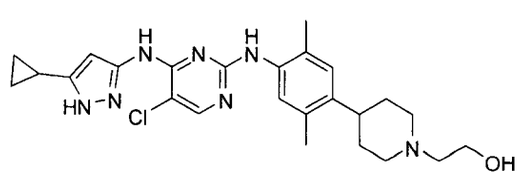
 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino) pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol	 5-cloro-N2-(4-(1-((3,5-dimetil-isoxazol-4-il)-metil)-piperidin-2-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 3-(4-(5-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2-fluoro-4-metil-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-hidroxi-ciclopropil)-metanona
	

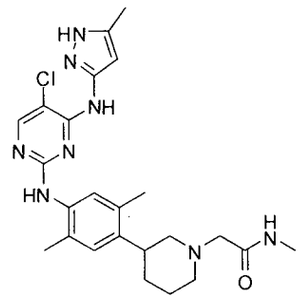
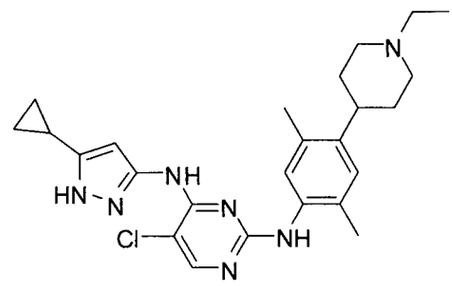
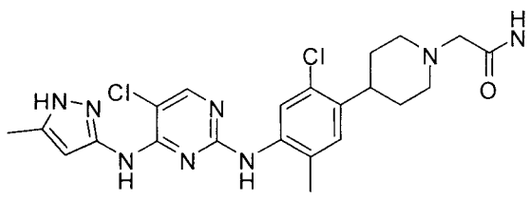
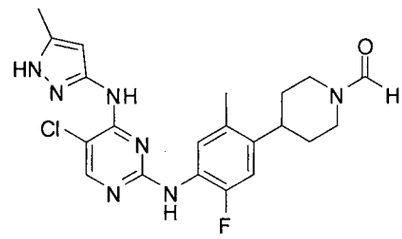
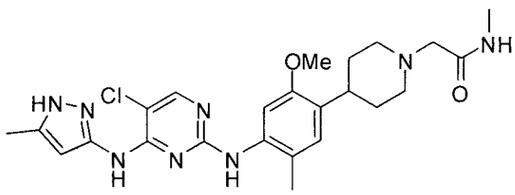
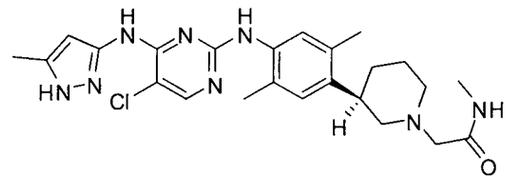
2-(4-(4-(5-cloro-4-(5-ciclopropil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-N-metil-acetamida	(2-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(1-hidroxi-ciclopropil)-metanona
 2-(4-(4-(5-cloro-4-(5-ciclopropil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida	 5-cloro-N2-(2,5-dimetil-4-(1-(3-morfolinopropil-sulfonil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 2-(4-(4-(5-cloro-4-(5-ciclopropil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-	

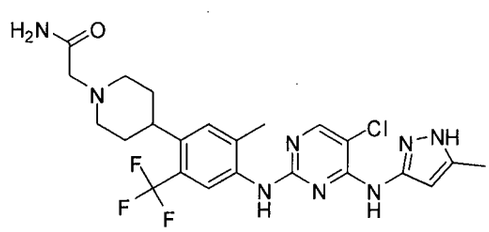
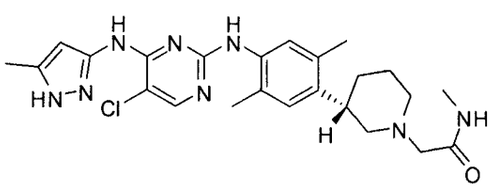
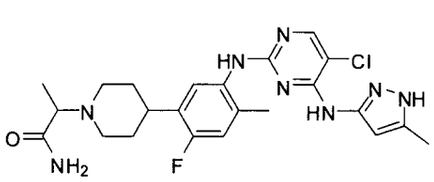
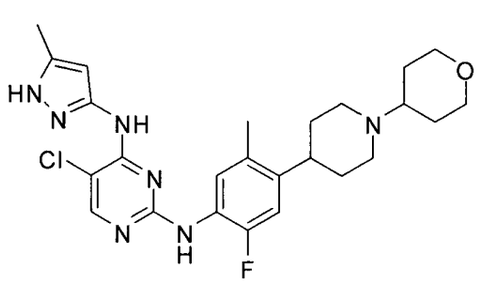
fenil)-piperidin-1-il)-acetamida	N2-(4-(1-(3-(azetidin-1-il)-propil-sulfonil)-piperidin-4-il)-2,5-dimetil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 2-(4-(4-(5-cloro-4-(5-ciclopropil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-acetamida	 (3R,4R)-1-(3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il-sulfonil)-propil)-pirrolidin-3,4-diol
	

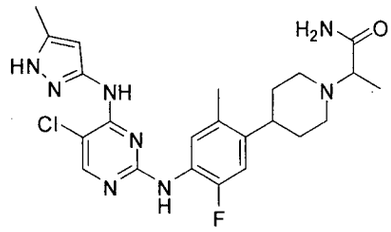
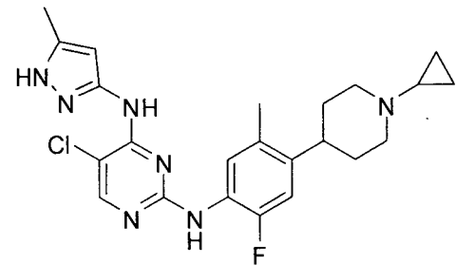
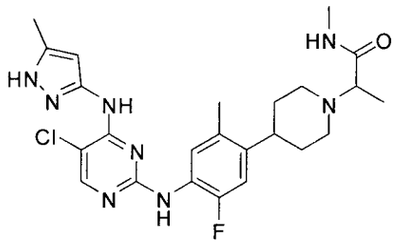
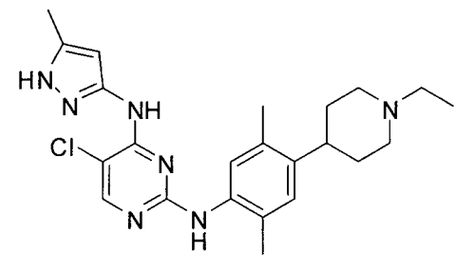
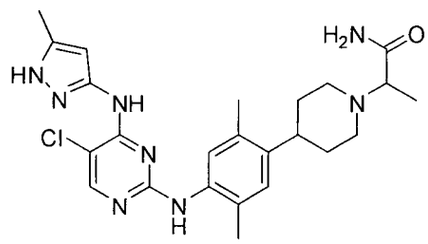
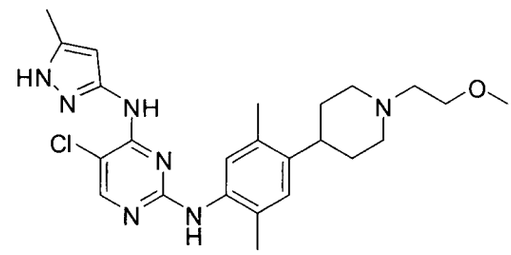
2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-(trifluoro-metil)-fenil)-piperidin-1-il)-acetamida	(2S)-3-(2-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol
 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-acetamida	 1-((4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-metil)-ciclopropan-carbonitrilo
 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-acetonitrilo

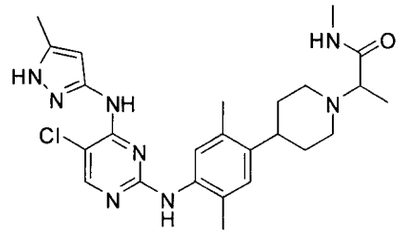
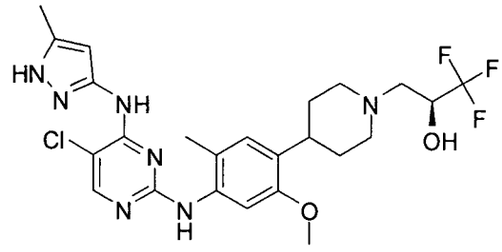
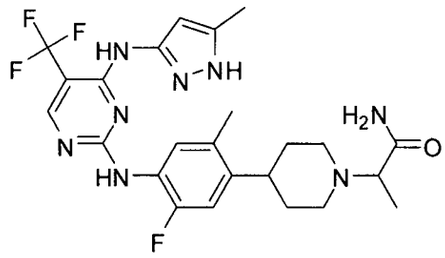
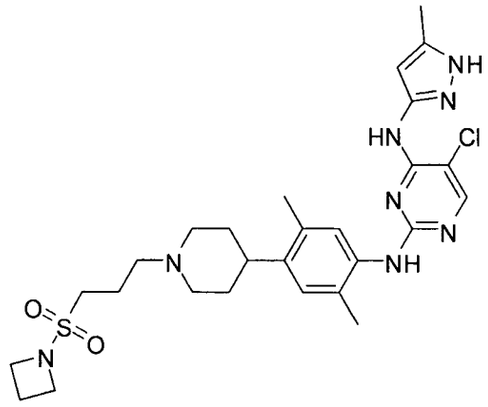
 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-acetamida	 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propano-nitrilo
 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-acetamida	 (2S)-3-(3-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol
 2-(3-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-	 2-(4-(2,5-dimetil-4-(4-(5-metil-

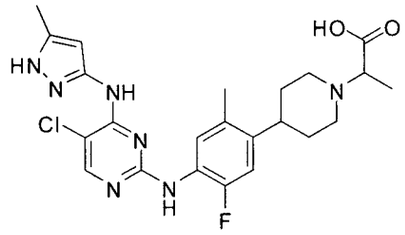
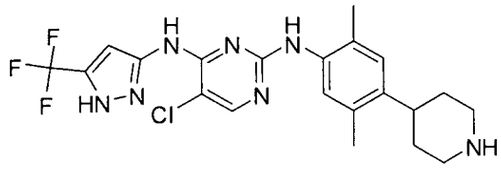
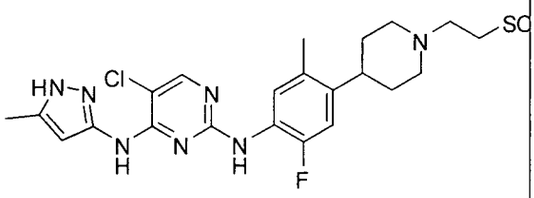
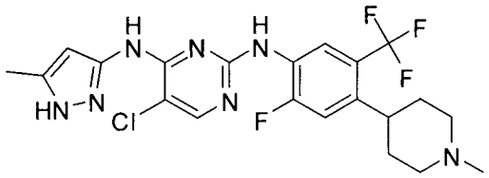
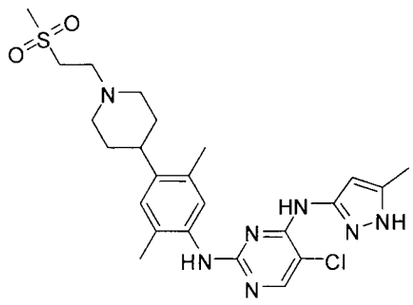
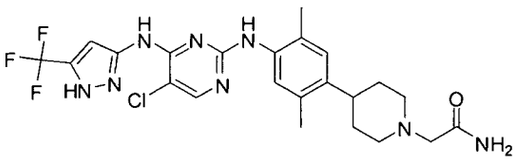
amino)-2,5-dimetil-fenil)-piperidin-1-il)-acetamida	1H-pirazol-3-il-amino)-5-(trifluoro-metil)-pirimidin-2-il-amino)-fenil)-piperidin-1-il)-acetamida
 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-N-metil-acetamida	 2-(4-(2,5-dimetil-4-(4-(5-metil-1H-pirazol-3-il-amino)-5-(trifluoro-metil)-pirimidin-2-il-amino)-fenil)-piperidin-1-il)-N-metil-acetamida
 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida	 2-(4-(4-(5-cloro-4-(5-ciclopropil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-etanol

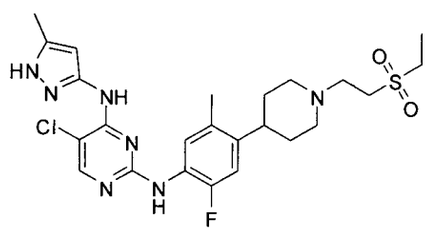
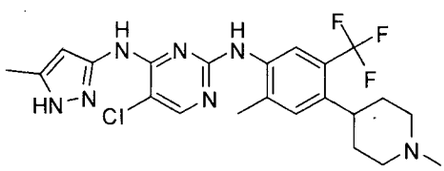
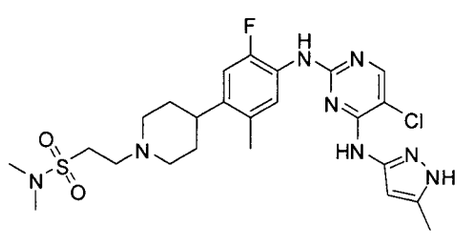
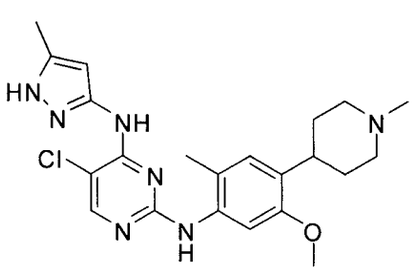
 2-(3-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida	 5-cloro-N4-(5-ciclopropil-1H-pirazol-3-il)-N2-(4-(1-etil-piperidin-4-il)-2,5-dimetil-fenil)-pirimidin-2,4-diamina
 2-(4-(2-cloro-4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-metil-fenil)-piperidin-1-il)-N-metil-acetamida	 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-carbaldehído
 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-	 (R)-2-(3-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-

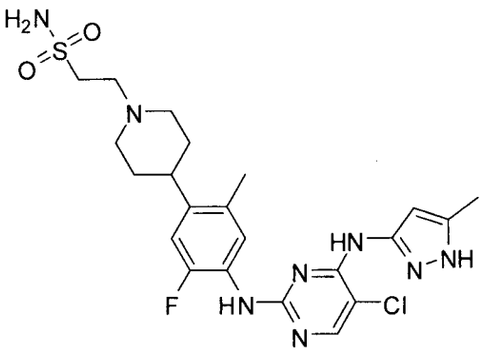
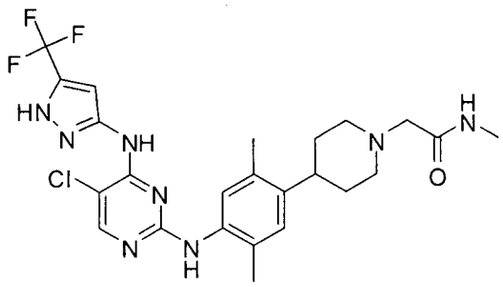
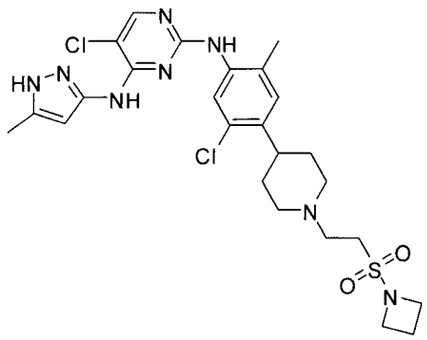
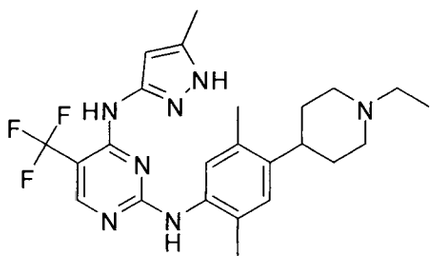
amino)-2-metoxi-5-metil-fenil)-piperidin-1-il)-N-metil-acetamida	2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida
 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-metil-2-(trifluoro-metil)-fenil)-piperidin-1-il)-acetamida	 (S)-2-(3-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida
 2-(4-(5-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2-fluoro-4-metil-fenil)-piperidin-1-il)-propanamida	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(tetrahidro-2H-piran-4-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

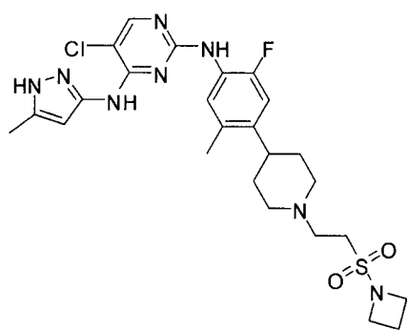
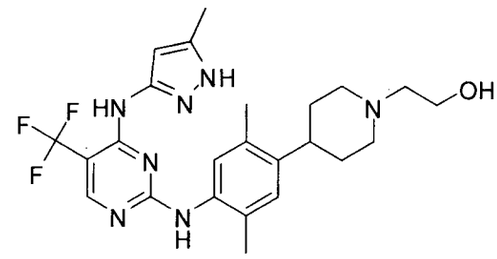
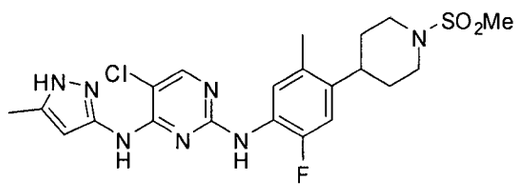
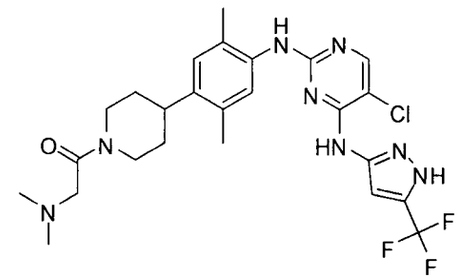
 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propanamida	 5-cloro-N2-(4-(1-ciclopropil-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-N-metil-propanamida	 5-cloro-N2-(4-(1-etil-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 2-(4-(4-(5-cloro-4-(5-metil-1H-	 5-cloro-N2-(4-(1-(2-metoxi-etil)-

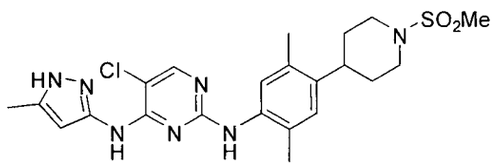
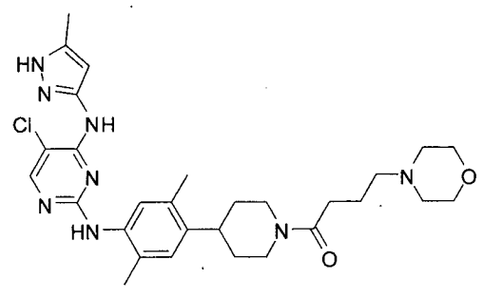
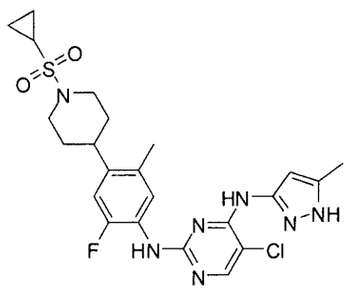
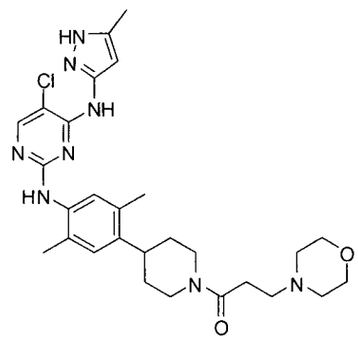
pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-propanamida	piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-propanamida	 (S)-3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2-metoxi-5-metil-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol
 2-(4-(5-fluoro-2-metil-4-(4-(5-metil-1H-pirazol-3-il-amino)-5-(trifluoro-metil)-pirimidin-2-il-amino)-fenil)-piperidin-1-il)-propanamida	 N2-(4-(1-(3-(azetidin-1-il-sulfonil)-propil)-piperidin-4-il)-2,5-dimetil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-

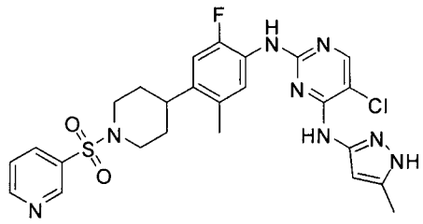
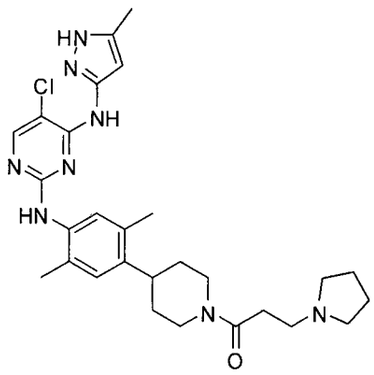
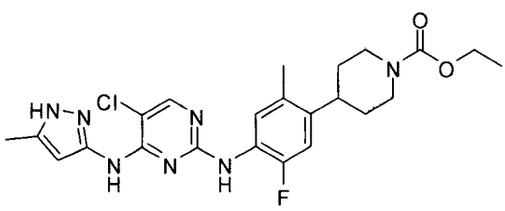
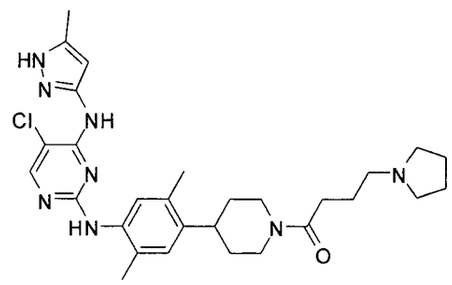
	2,4-diamina
 ácido 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propanoico	 5-cloro-N2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-N4-(5-(trifluoro-metil)-1H-pirazol-3-il)-pirimidin-2,4-diamina
 5-cloro-N2-(2-fluoro-5-metil-4-(1-(2-(metil-sulfonil)-etil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 5-cloro-N2-(2-fluoro-4-(1-metil-piperidin-4-il)-5-(trifluoro-metil)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
	 2-(4-(4-(5-cloro-4-(5-(trifluoro-metil)-1H-pirazol-3-il-amino)-

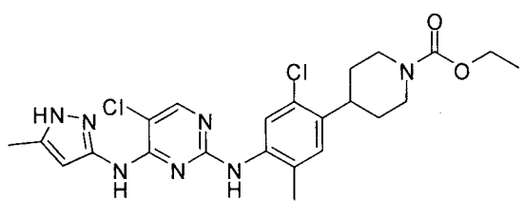
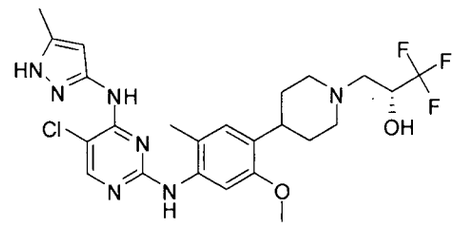
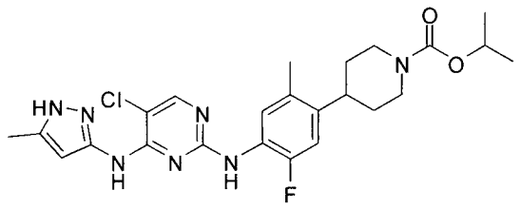
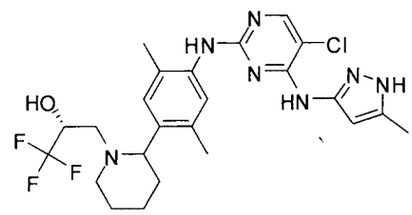
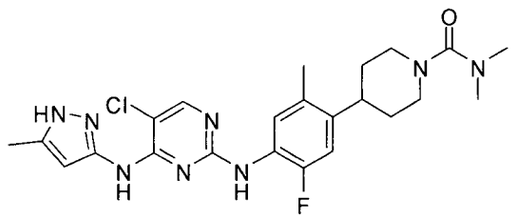
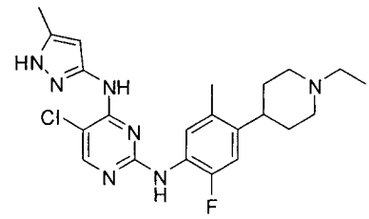
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 5-cloro-N2-(4-(1-(2-(etil-sulfonil)-etil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 5-cloro-N4-(5-metil-1H-pirazol-3-il)-N2-(2-metil-4-(1-metil-piperidin-4-il)-5-(trifluoro-metil)-fenil)-pirimidin-2,4-diamina
 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-N,N-dimetil-etan-sulfonamida	 5-cloro-N2-(5-metoxi-2-metil-4-(1-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

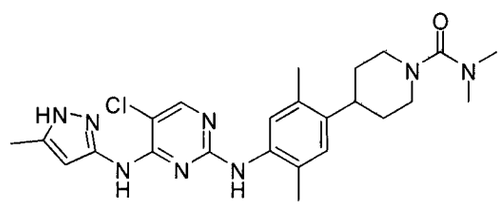
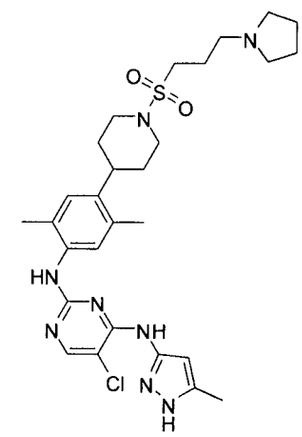
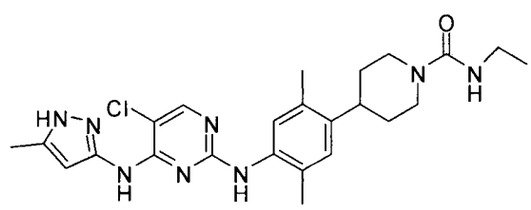
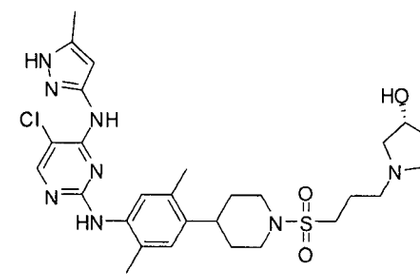
 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-etan-sulfonamida	 2-(4-(4-(5-cloro-4-(5-(trifluoro-metil)-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-N-metil-acetamida
 N2-(4-(1-(2-(azetidin-1-il-sulfonil)-etil)-piperidin-4-il)-5-cloro-2-metil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 N2-(4-(1-etil-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-5-(trifluoro-metil)-pirimidin-2,4-diamina

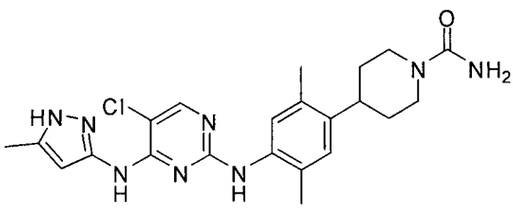
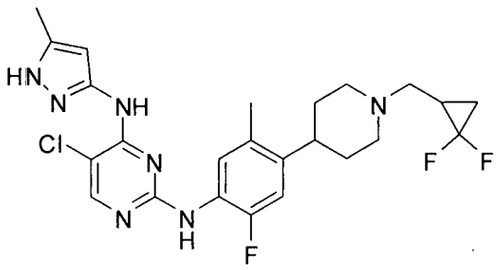
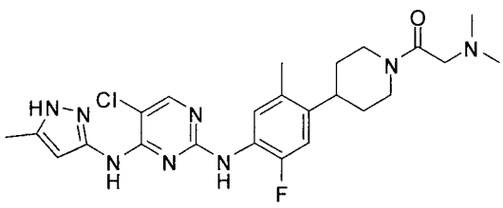
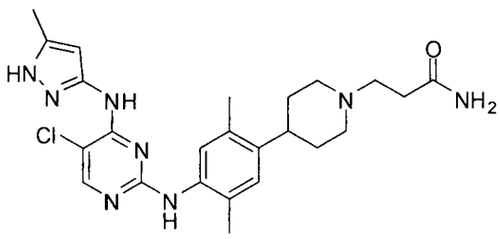
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 5-cloro-N2-(2-fluoro-5-metil-4-(1-(metil-sulfonil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 1-(4-(4-(5-cloro-4-(5-(trifluoro-metil)-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona

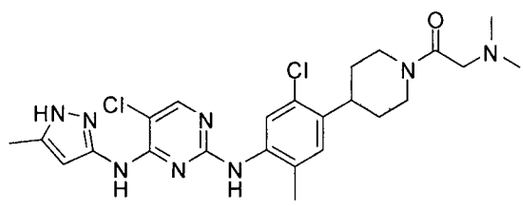
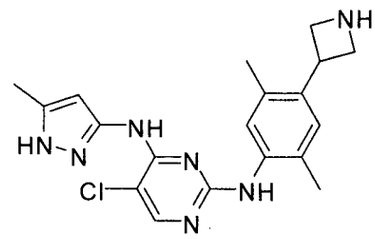
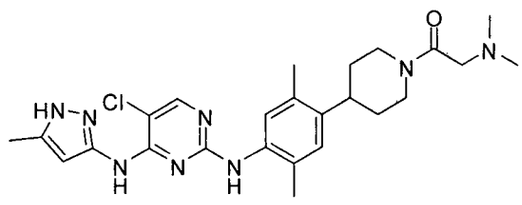
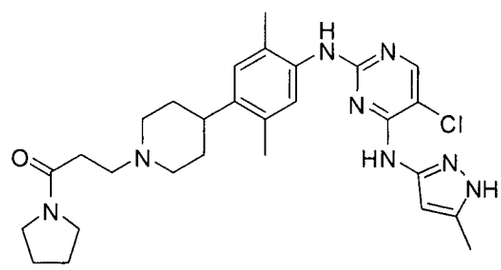
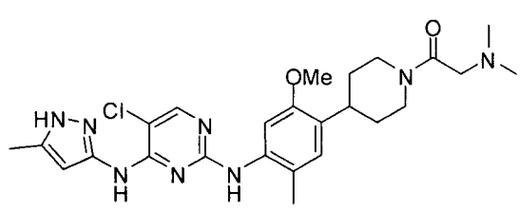
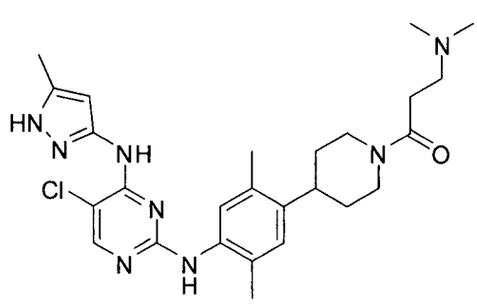
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 5-cloro-N2-(4-(1-(ciclopropil-sulfonil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-3-morfolino-propan-1-ona

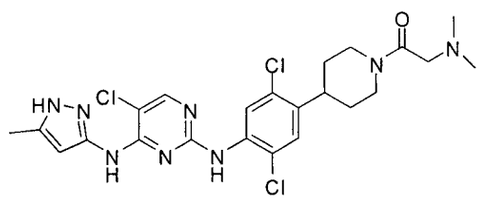
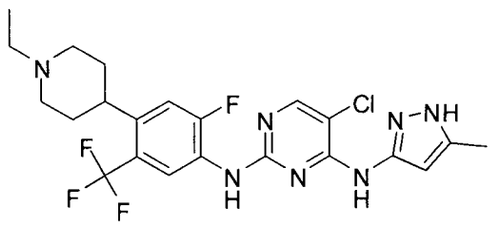
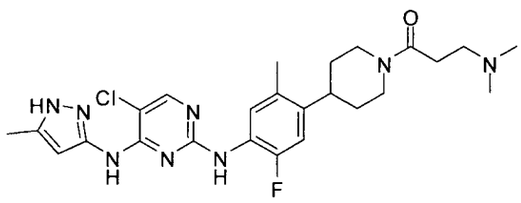
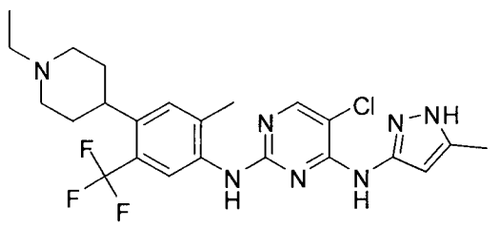
 5-cloro-N2-(2-fluoro-5-metil-4-(1-(piridin-3-il-sulfonil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-3-(pirrolidin-1-il)-propan-1-ona
 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-carboxilato de etilo	 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-4-(pirrolidin-1-il)-butan-1-ona

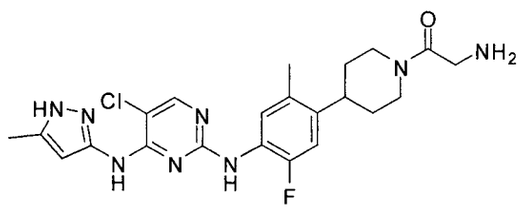
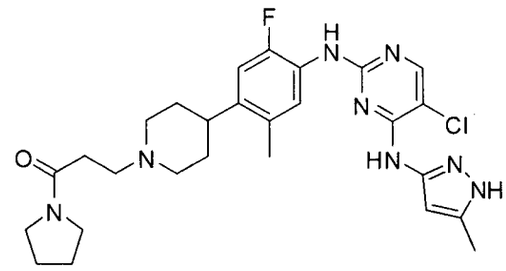
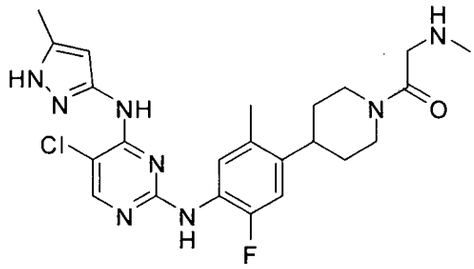
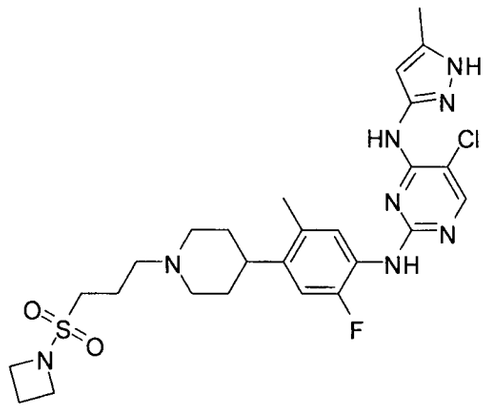
 4-(2-cloro-4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-metil-fenil)-piperidin-1-carboxilato de etilo	 (R)-3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2-metoxi-5-metil-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol
 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-carboxilato de isopropilo	 (2R)-3-(2-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-1,1,1-trifluoro-propan-2-ol
 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-	 5-cloro-N2-(4-(1-etil-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-

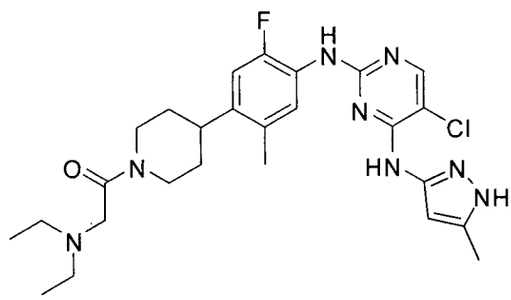
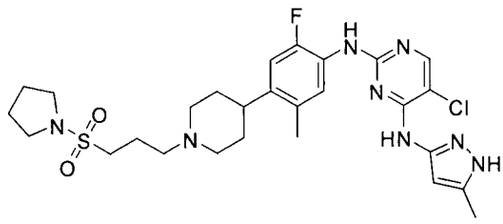
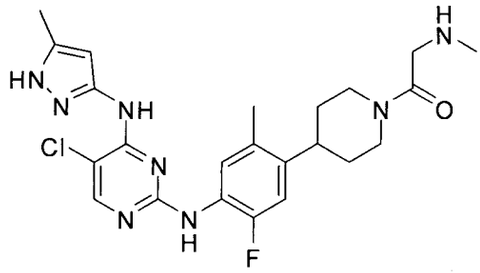
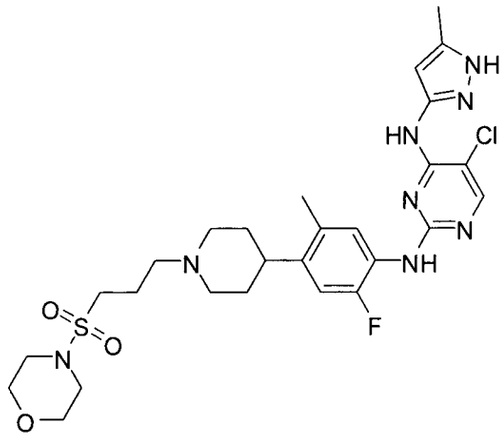
amino)-5-fluoro-2-metil-fenil)-N,N-dimetil-piperidin-1-carboxamida	metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-N,N-dimetil-piperidin-1-carboxamida	 5-cloro-N2-(2,5-dimetil-4-(1-(3-(pirrolidin-1-il)-propil-sulfonil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-N-etil-piperidin-1-carboxamida	 (R)-1-(3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il-sulfonil)-

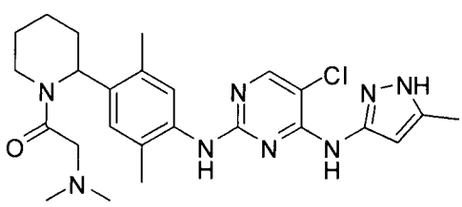
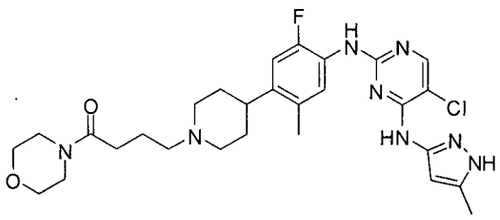
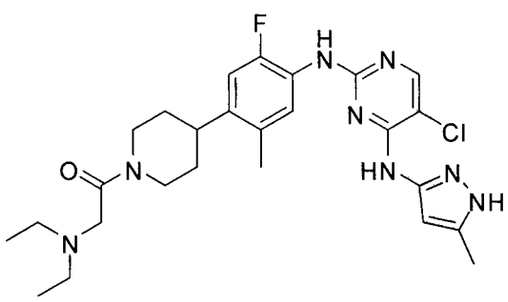
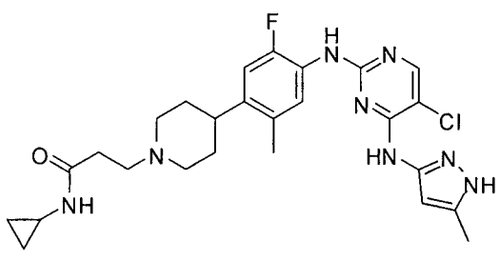
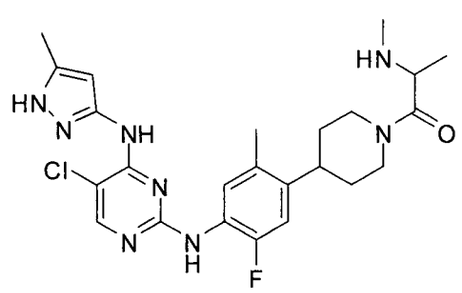
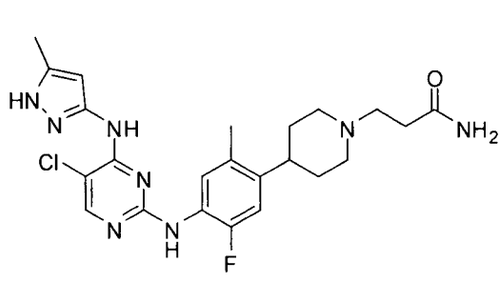
	propil)-pirrolidin-3-ol
 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-carboxamida	 5-cloro-N2-(4-(1-((2,2-difluoro-ciclopropil)-metil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona	 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-propanamida

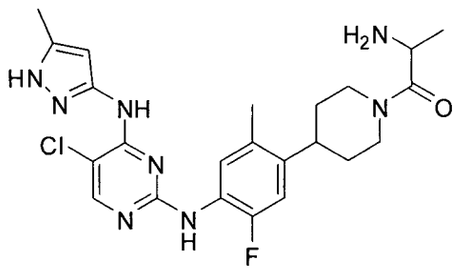
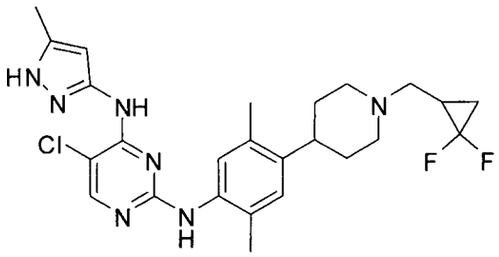
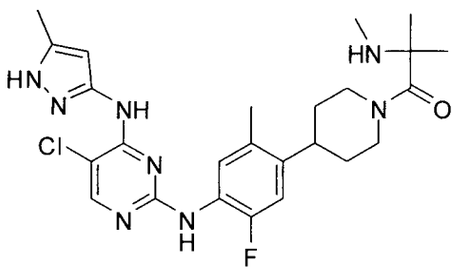
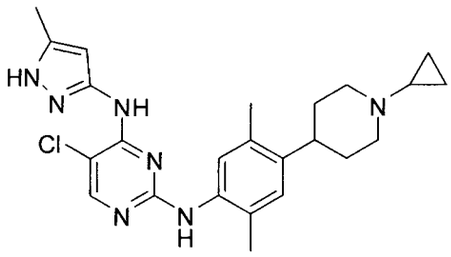
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 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona	 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-1-(pirrolidin-1-il)-propan-1-ona
 1-(4-(4-(5-cloro-4-(5-metil-1H-	

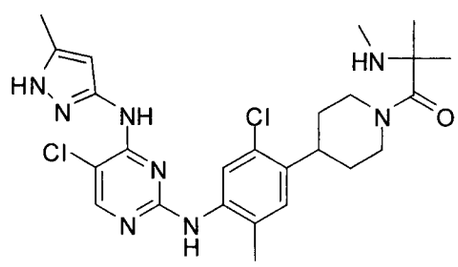
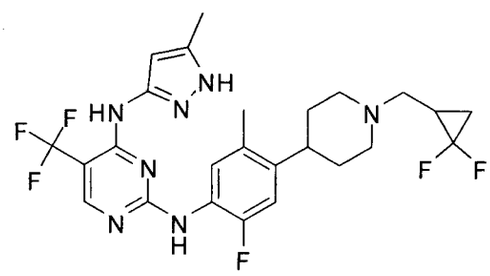
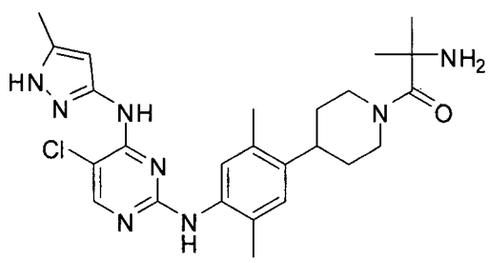
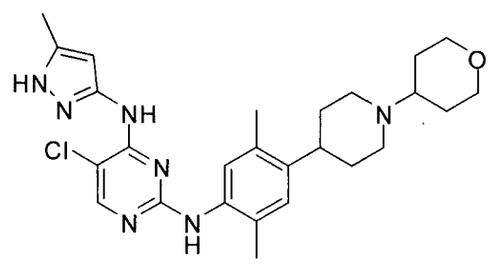
pirazol-3-il-amino)-pirimidin-2-il-amino)-2-metoxi-5-metil-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona	1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-3-(dimetil-amino)-propan-1-ona
 1-(4-(2,5-dicloro-4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona	 5-cloro-N2-(4-(1-etil-piperidin-4-il)-2-fluoro-5-(trifluoro-metil)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-3-(dimetil-amino)-propan-1-ona	 5-cloro-N2-(4-(1-etil-piperidin-4-il)-2-metil-5-(trifluoro-metil)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

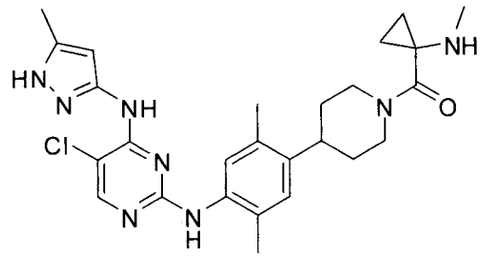
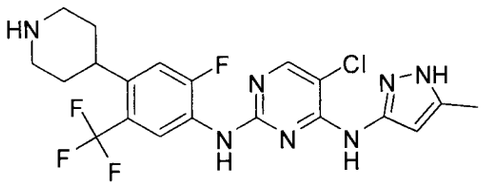
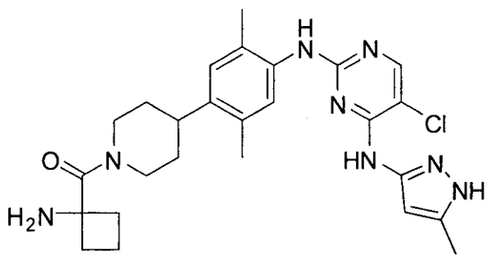
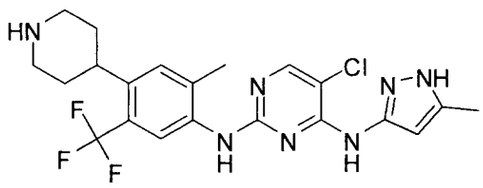
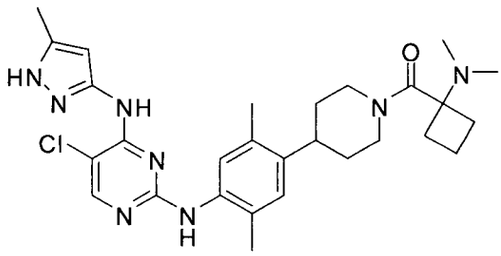
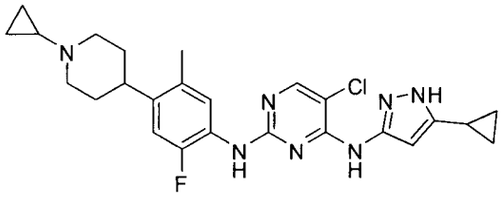
	
2-amino-1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-etanona	3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-1-(pirrolidin-1-il)-propan-1-ona
	
1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(metil-amino)-etanona	N2-(4-(1-(3-(azetidin-1-il-sulfonil)-propil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

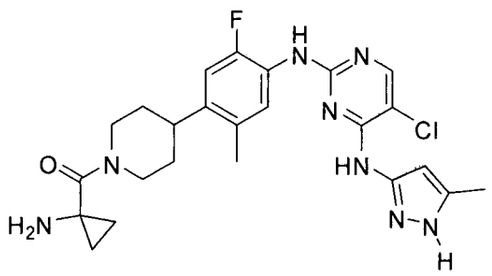
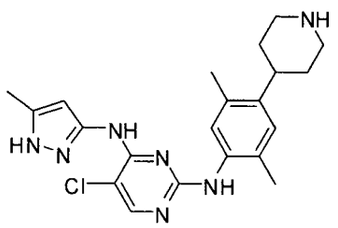
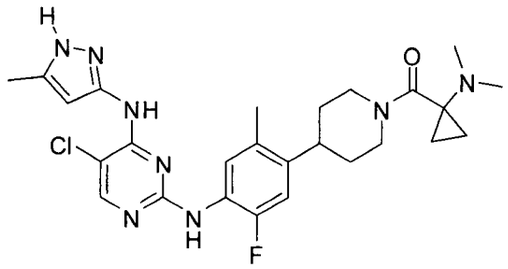
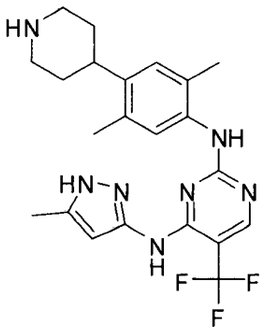
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(dietil-amino)-etanona	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(3-(pirrolidin-1-il-sulfonil)-propil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(metil-amino)-etanona	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(3-(morfolino-sulfonil)-propil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

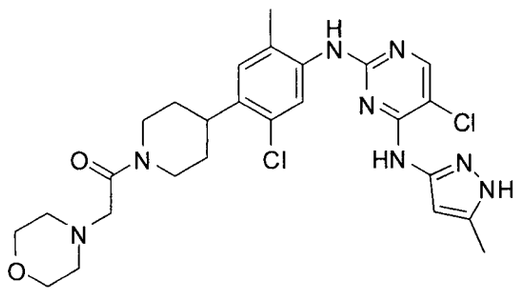
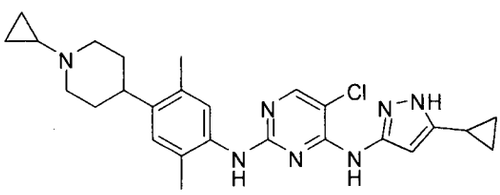
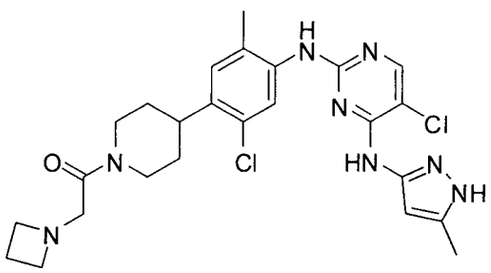
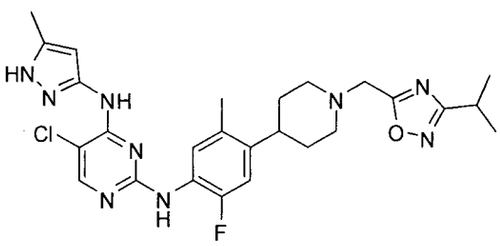
 1-(2-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(dimetil-amino)-etanona	 4-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-1-morfolinobutan-1-ona
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(dietil-amino)-etanona	 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-N-ciclopropil-propanamida
	

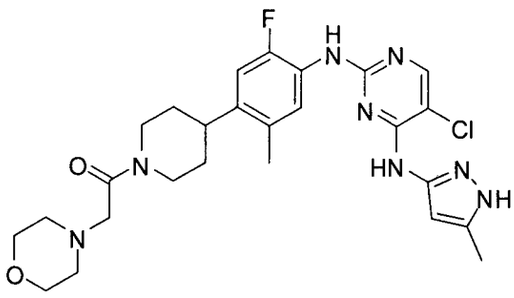
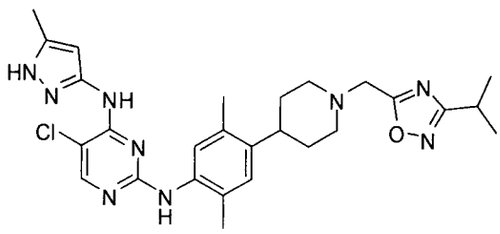
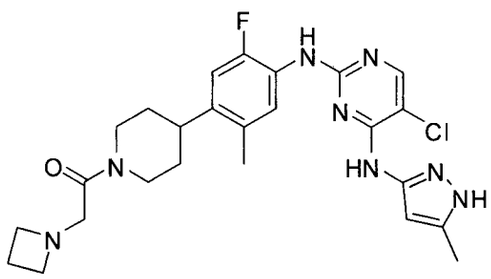
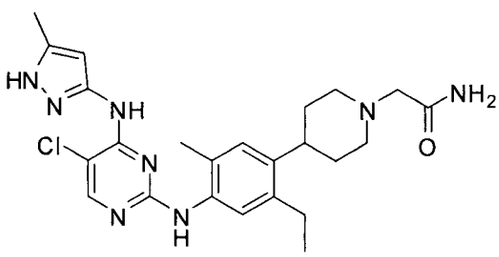
1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(metil-amino)-propan-1-ona	3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propanamida
 2-amino-1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-propan-1-ona	 5-cloro-N2-(4-(1-((2,2-difluoro-ciclopropil)-metil)-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-metil-2-(metil-	 5-cloro-N2-(4-(1-ciclopropil-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

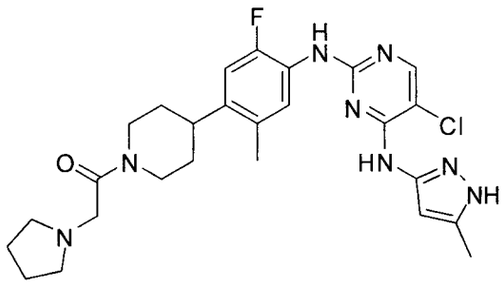
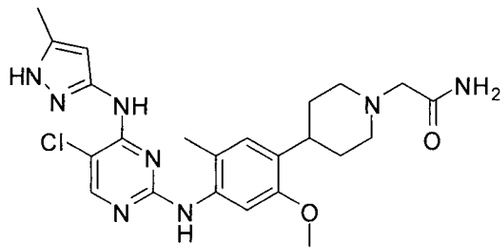
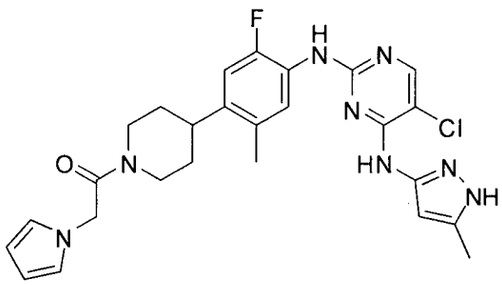
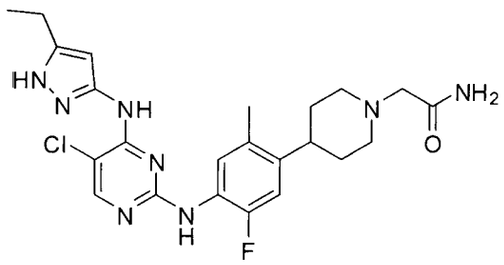
amino)-propan-1-ona	
 1-(4-(2-cloro-4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-metil-fenil)-piperidin-1-il)-2-metil-2-(metil-amino)-propan-1-ona	 N2-(4-(1-((2,2-difluoro-ciclopropil)-metil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-5-(trifluoro-metil)-pirimidin-2,4-diamina
 2-amino-1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-metil-propan-1-ona	 5-cloro-N2-(2,5-dimetil-4-(1-(tetrahidro-2H-piran-4-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

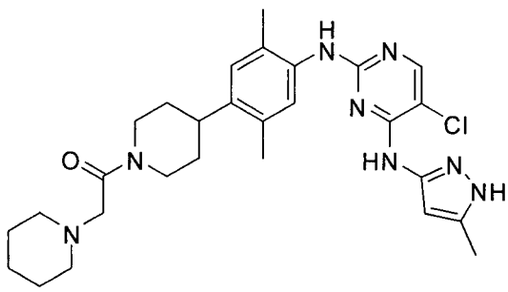
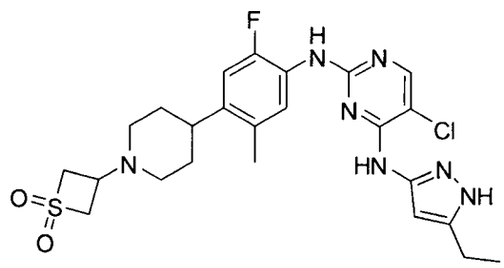
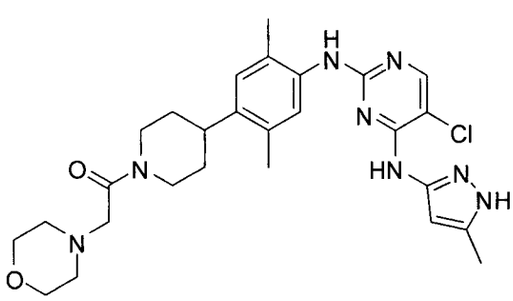
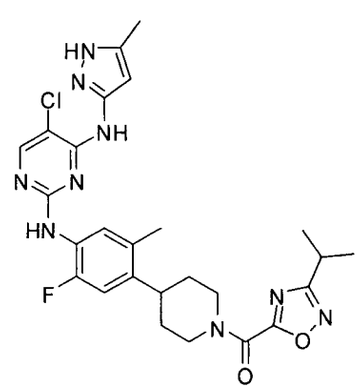
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(1-(metil-amino)-ciclopropil)-metanona	 5-cloro-N2-(2-fluoro-4-(piperidin-4-il)-5-(trifluoro-metil)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 (1-amino-ciclobutil)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-metanona	 5-cloro-N4-(5-metil-1H-pirazol-3-il)-N2-(2-metil-4-(piperidin-4-il)-5-(trifluoro-metil)-fenil)-pirimidin-2,4-diamina
	 5-cloro-N4-(5-ciclopropil-1H-

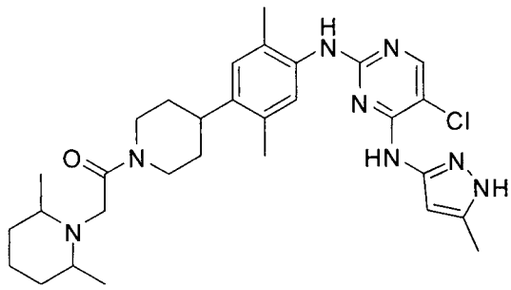
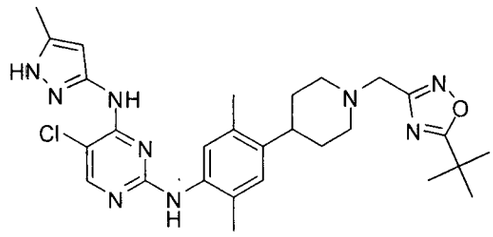
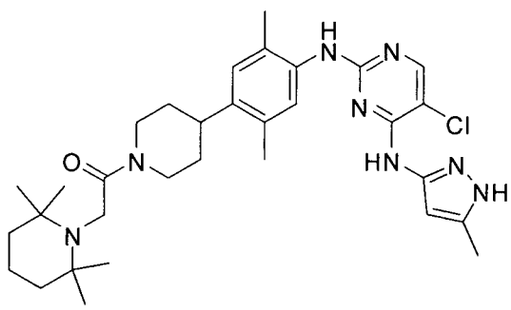
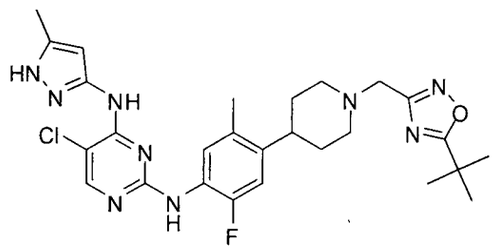
(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(1-(dimetil-amino)-ciclobutil)-metanona	pirazol-3-il)-N2-(4-(1-ciclopropil-piperidin-4-il)-2-fluoro-5-metil-fenil)-pirimidin-2,4-diamina
 (1-amino-ciclopropil)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-metanona	 5-cloro-N2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-(dimetil-amino)-	 N2-(2,5-dimetil-4-(piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-5-(trifluoro-metil)-pirimidin-

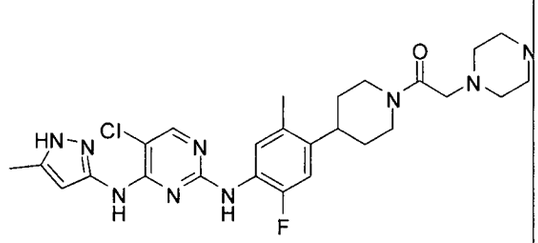
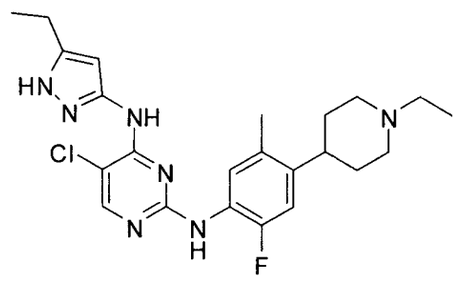
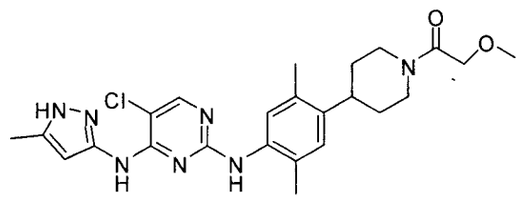
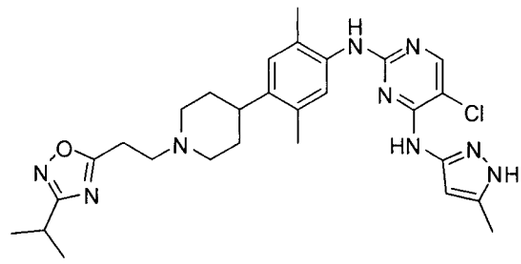
ciclopropil)-metanona	2,4-diamina
 1-(4-(2-cloro-4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-metil-fenil)-piperidin-1-il)-2-morfolino-etanona	 5-cloro-N4-(5-ciclopropil-1H-pirazol-3-il)-N2-(4-(1-ciclopropil-piperidin-4-il)-2,5-dimetil-fenil)-pirimidin-2,4-diamina
 2-(azetidin-1-il)-1-(4-(2-cloro-4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-metil-fenil)-piperidin-1-il)-etanona	 5-cloro-N2-(2-fluoro-4-(1-((3-isopropil-1,2,4-oxadiazol-5-il)-metil)-piperidin-4-il)-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

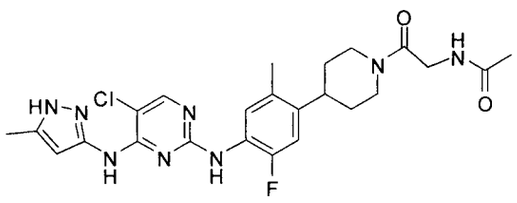
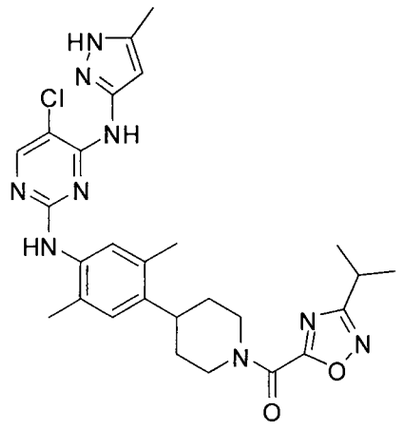
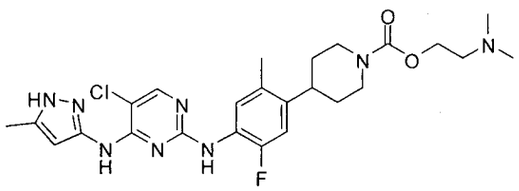
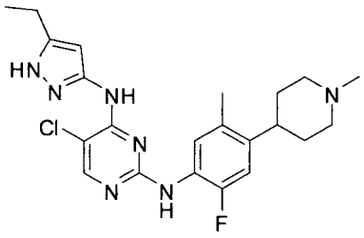
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-morfolino-etanona	 5-cloro-N2-(4-(1-((3-isopropil-1,2,4-oxadiazol-5-il)-metil)-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 2-(azetidin-1-il)-1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-etanona	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2-etil-5-metil-fenil)-piperidin-1-il)-acetamida

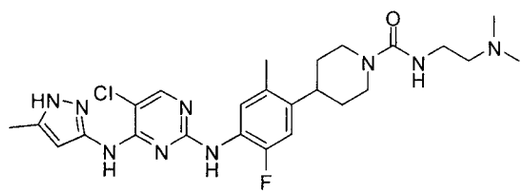
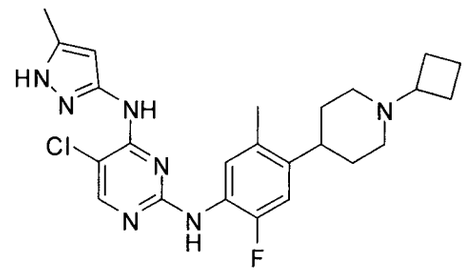
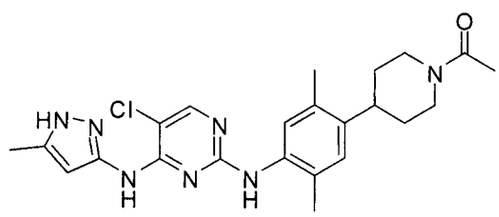
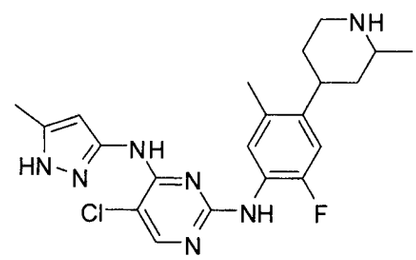
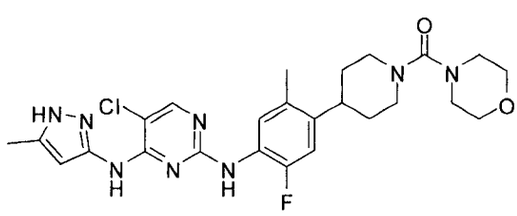
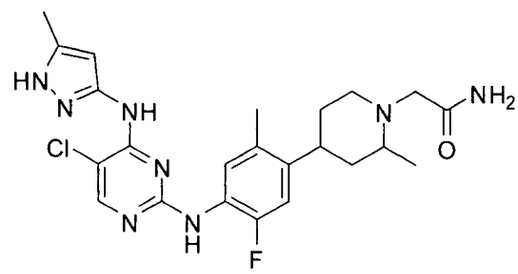
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(pirrolidin-1-il)-etanona	 2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2-metoxi-5-metil-fenil)-piperidin-1-il)-acetamida
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(1H-pirrol-1-il)-etanona	 2-(4-(4-(5-cloro-4-(5-etil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-acetamida

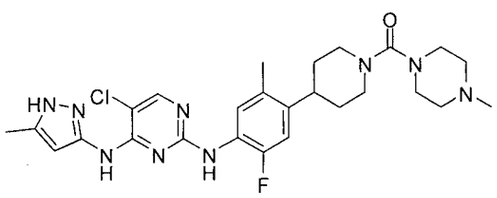
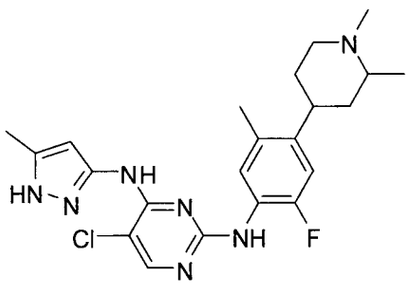
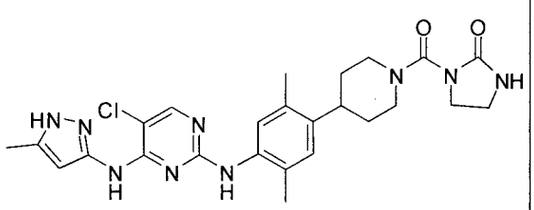
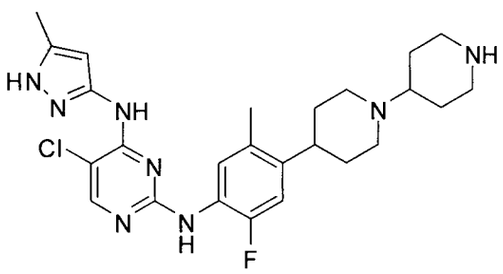
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(piperidin-1-il)-etanona	 5-cloro-N2-{4-[1-(1,1-dioxo-1λ6-tietan-3-il)-piperidin-4-il]-2-fluoro-5-metil-fenil}-N4-(5-etil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-morfolino-etanona	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(3-isopropil-1,2,4-oxadiazol-5-il)-metanona

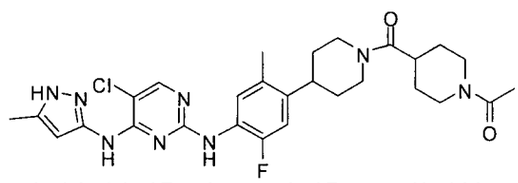
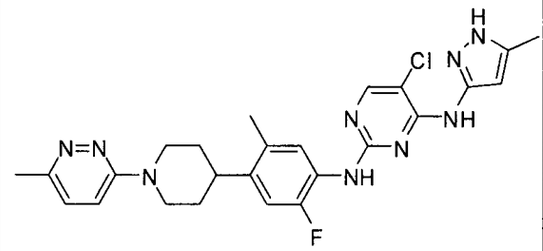
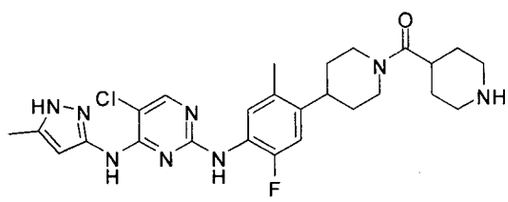
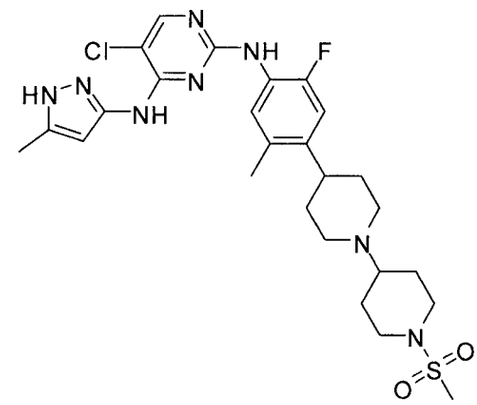
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(2,6-dimetil-piperidin-1-il)-etanona	 N2-(4-(1-((5-terbutil-1,2,4-oxadiazol-3-il)-metil)-piperidin-4-il)-2,5-dimetil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-(2,2,6,6-tetrametil-piperidin-1-il)-etanona	 N2-(4-(1-((5-terbutil-1,2,4-oxadiazol-3-il)-metil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

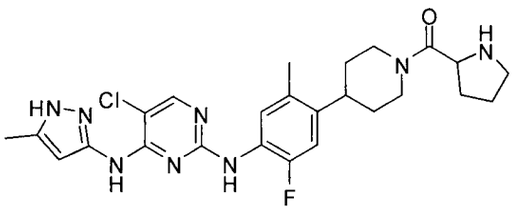
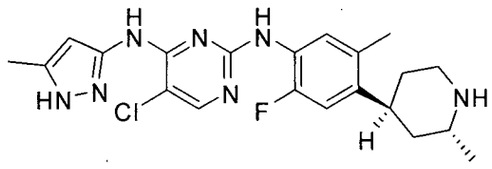
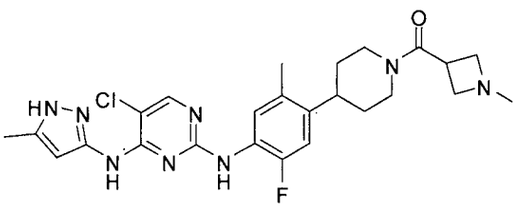
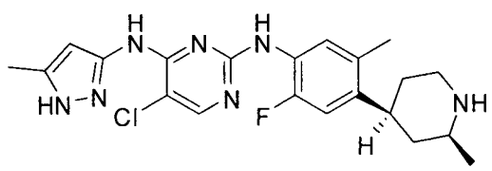
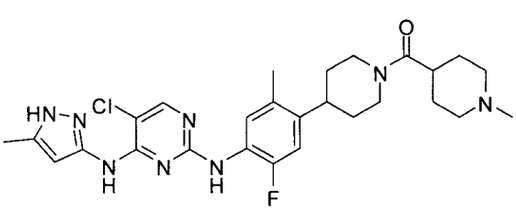
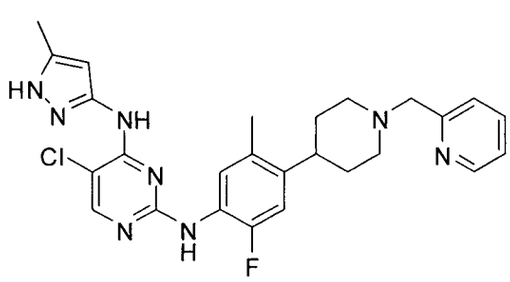
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-(4-metil-piperazin-1-il)-etanona	 5-cloro-N4-(5-etil-1H-pirazol-3-il)-N2-(4-(1-etil-piperidin-4-il)-2-fluoro-5-metil-fenil)-pirimidin-2,4-diamina
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-metoxi-etanona	 5-cloro-N2-(4-(1-(2-(3-isopropil-1,2,4-oxadiazol-5-il)-etil)-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

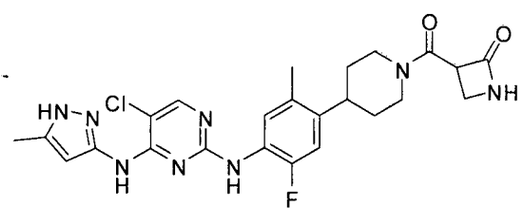
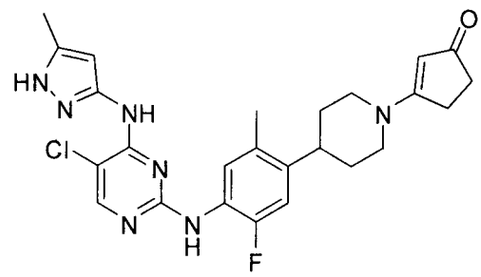
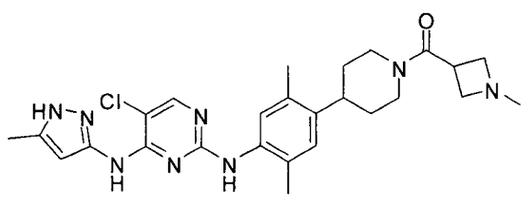
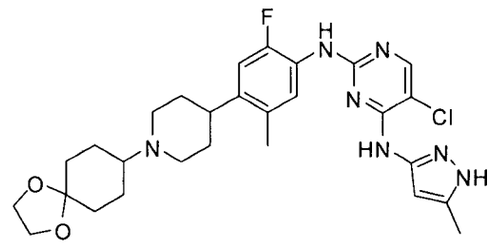
 N-(2-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-2-oxoetil)-acetamida	 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(3-isopropil-1,2,4-oxadiazol-5-il)-metanona
 2-(dimetil-amino)-4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-carboxilato de etilo	 5-cloro-N4-(5-etil-1H-pirazol-3-il)-N2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil)-pirimidin-2,4-diamina

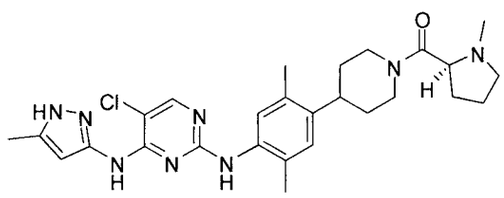
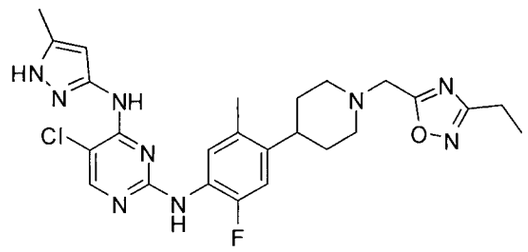
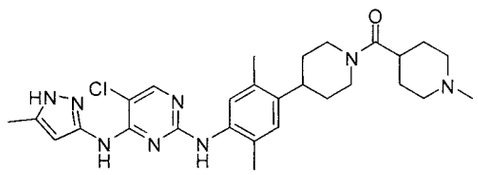
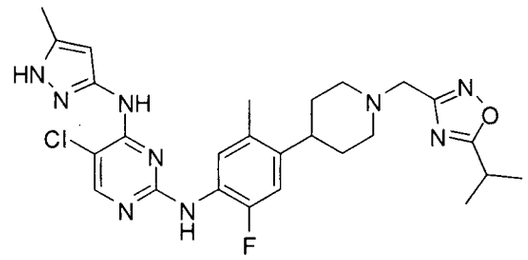
 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-N-(2-(dimetil-amino)-etil)-piperidin-1-carboxamida	 5-cloro-N2-(4-(1-ciclobutil-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-etanona	 5-cloro-N2-(2-fluoro-5-metil-4-(2-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-	 2-(4-(4-(5-cloro-4-(5-metil-1H-

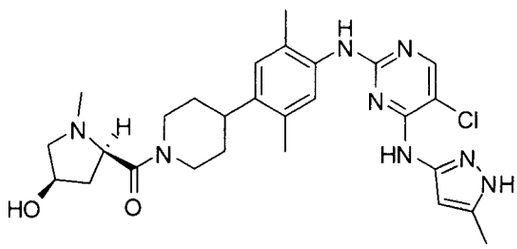
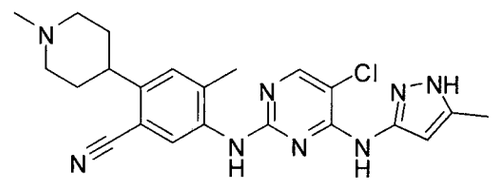
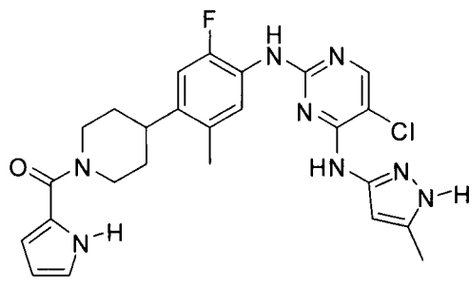
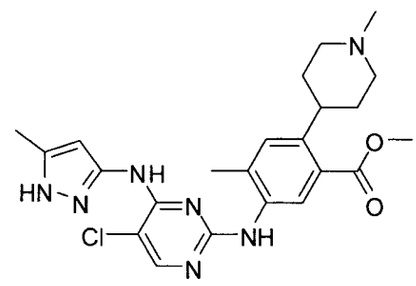
amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(morfolino)-metanona	pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-2-metil-piperidin-1-il)-acetamida
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(4-metil-piperazin-1-il)-metanona	 5-cloro-N2-(4-(1,2-dimetil-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-carbonil)-imidazolidin-2-ona	 N2-(4-(1,4'-bipiperidin-4-il)-2-fluoro-5-metil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

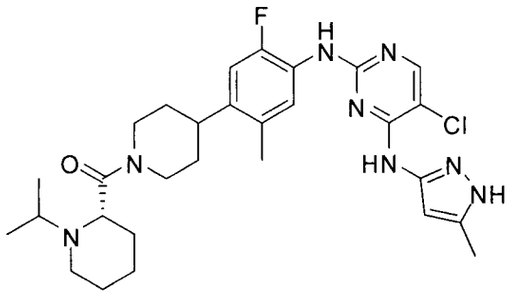
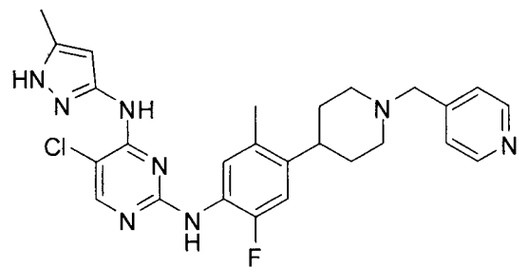
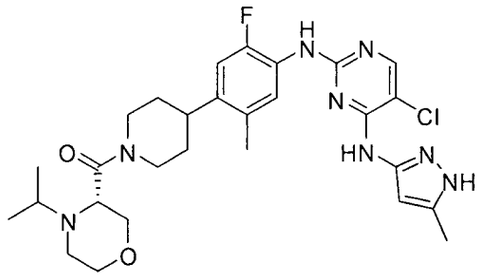
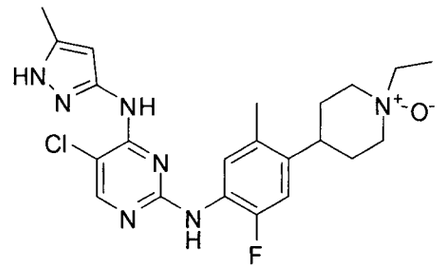
 1-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-2-metoxi-etanona	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(6-metil-piridazin-3-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(piperidin-4-il)-metanona	 5-cloro-N2-(2-fluoro-5-metil-4-(1'-(metil-sulfonil)-1,4'-bipiperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

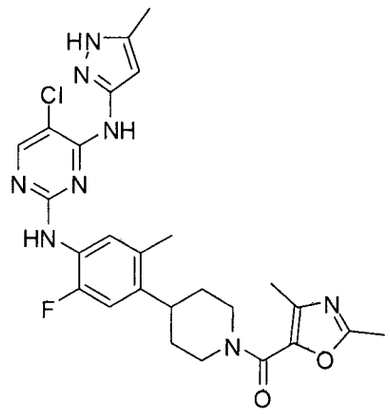
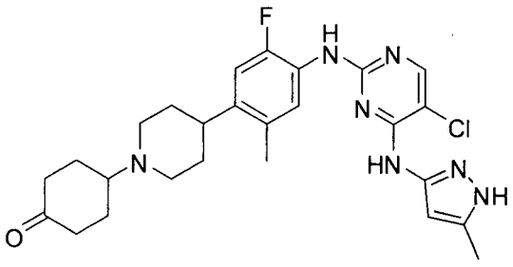
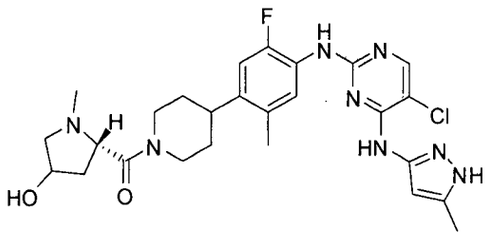
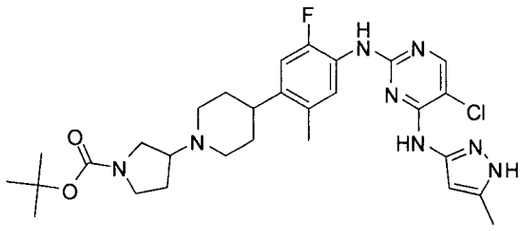
 (S)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(pirrolidin-2-il)-metanona	 5-cloro-N2-(2-fluoro-5-metil-4-((trans)-2-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-metilazetidin-3-il)-metanona	 5-cloro-N2-(2-fluoro-5-metil-4-((cis)-2-metil-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 (4-(4-(5-cloro-4-(5-metil-1H-	 5-cloro-N2-(2-fluoro-5-metil-4-(1-

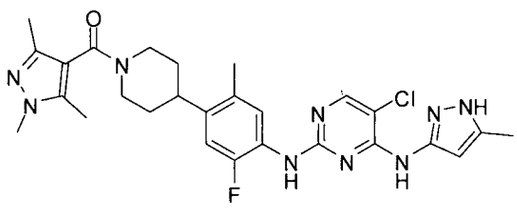
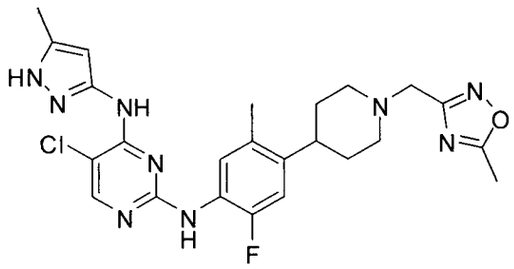
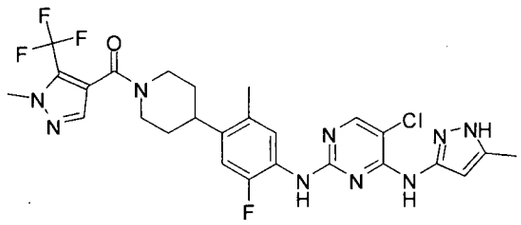
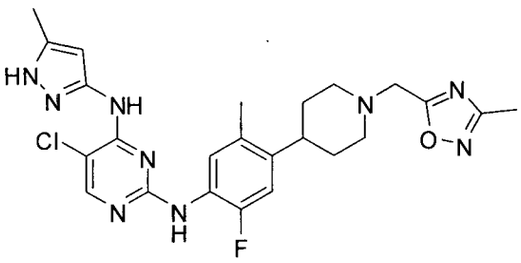
pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-metil-piperidin-4-il)-metanona	(piridin-2-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-carbonil)-azetidin-2-ona	 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-ciclopent-2-enona
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(1-metilazetidin-3-il)-metanona	 N2-(4-(1-(1,4-dioxaespiro-[4.5]-decan-8-il)-piperidin-4-il)-2-fluoro-5-metil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

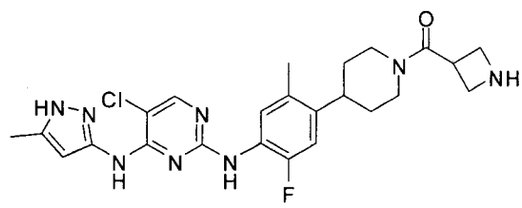
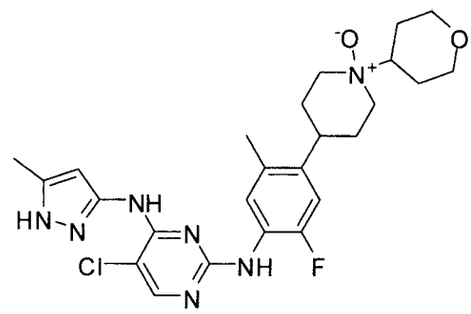
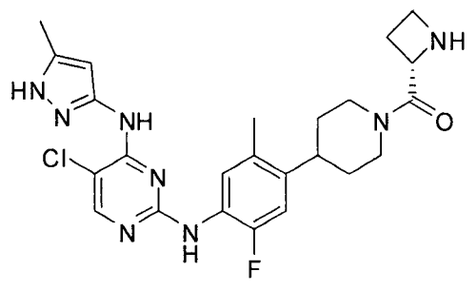
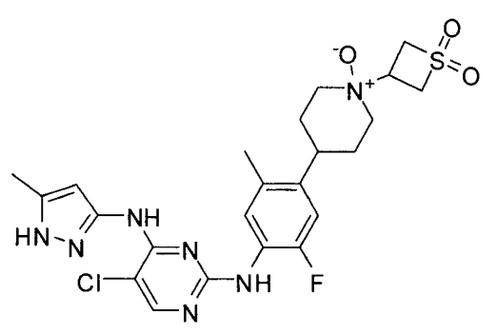
 (*S*)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(1-metil-pirrolidin-2-il)-metanona	 5-cloro-N2-(4-(1-((3-etil-1,2,4-oxadiazol-5-il)-metil)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(1-metil-piperidin-4-il)-metanona	 5-cloro-N2-(2-fluoro-4-(1-((5-isopropil-1,2,4-oxadiazol-3-il)-metil)-piperidin-4-il)-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

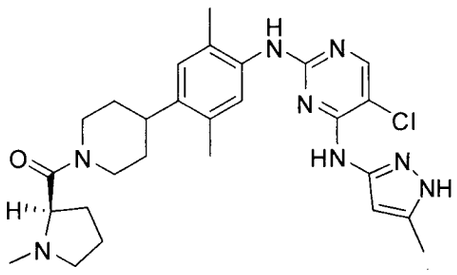
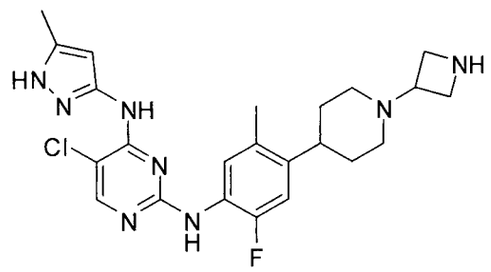
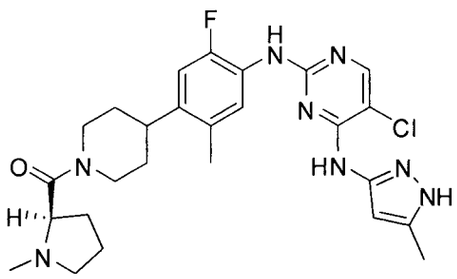
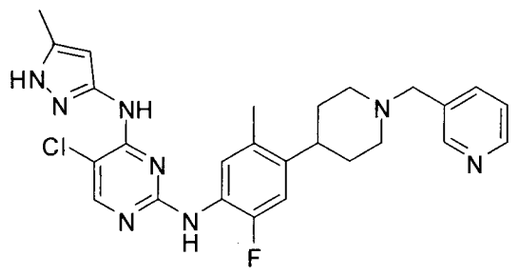
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-((2R,4R)-4-hidroxi-1-metil-pirrolidin-2-il)-metanona	 5-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-4-metil-2-(1-metil-piperidin-4-il)-benzonitrilo
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1H-pirrol-2-il)-metanona	 5-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-4-metil-2-(1-metil-piperidin-4-il)-benzoato de metilo

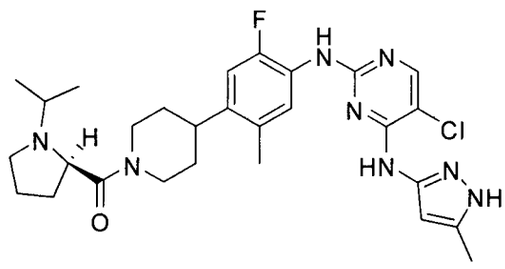
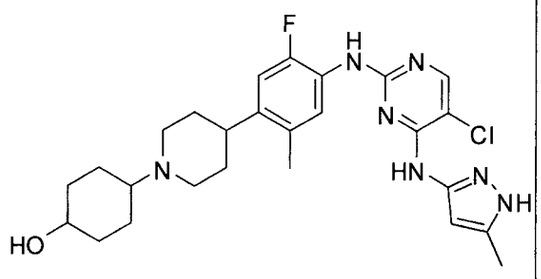
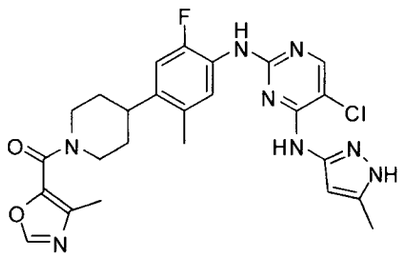
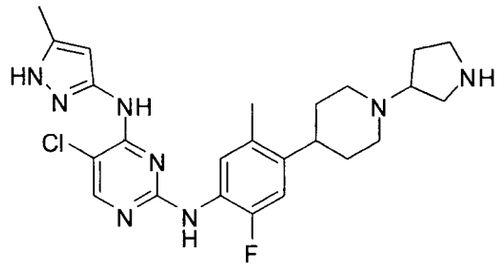
 (S)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-isopropil-piperidin-2-il)-metanona	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(piridin-4-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 (S)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(4-isopropil-morfolin-3-il)-metanona	 1-óxido de 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-1-etil-piperidina

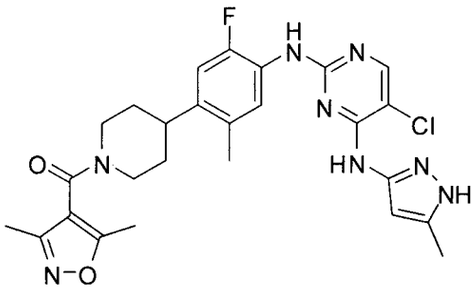
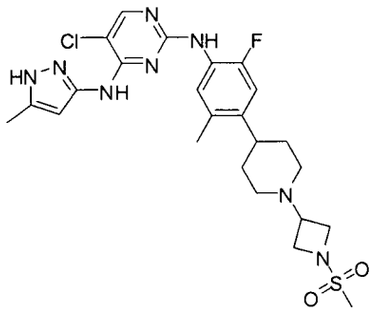
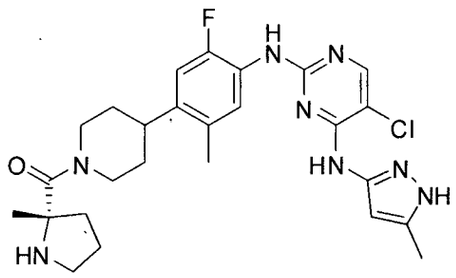
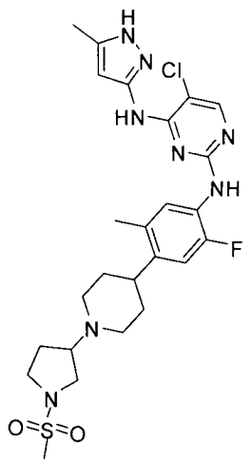
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(2,4-dimetil-oxazol-5-il)-metanona	 4-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-ciclohexanona
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-((2S)-4-hidroxi-1-metil-pirrolidin-2-il)-metanona	 3-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-pirrolidin-1-carboxilato de terbutilo

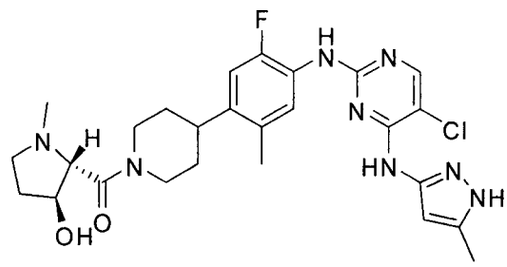
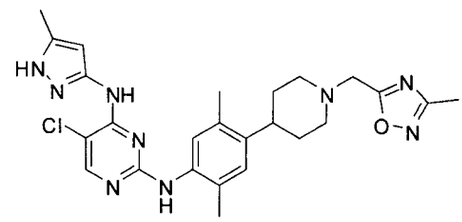
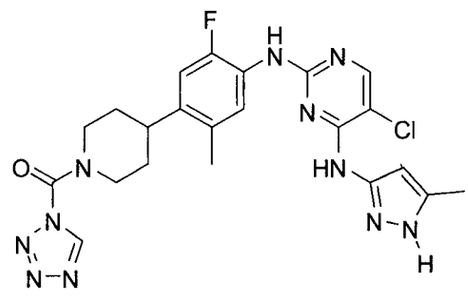
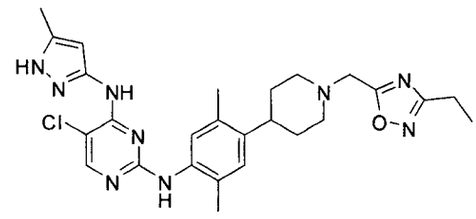
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1,3,5-trimetil-1H-pirazol-4-il)-metanona	 5-cloro-N2-(2-fluoro-5-metil-4-(1-((5-metil-1,2,4-oxadiazol-3-il)-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-metil-5-(trifluoro-metil)-1H-pirazol-4-il)-metanona	 5-cloro-N2-(2-fluoro-5-metil-4-(1-((3-metil-1,2,4-oxadiazol-5-il)-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

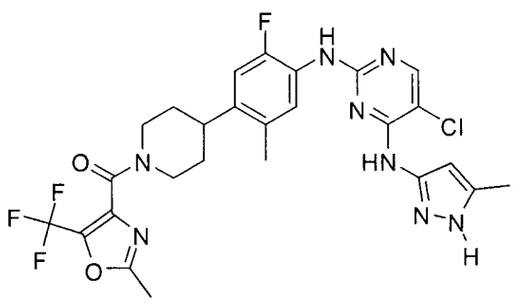
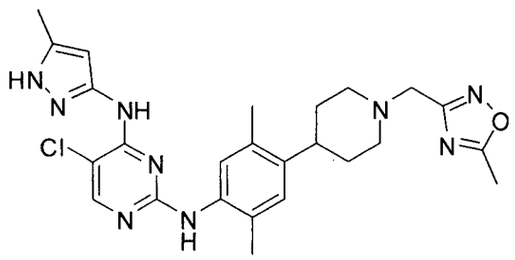
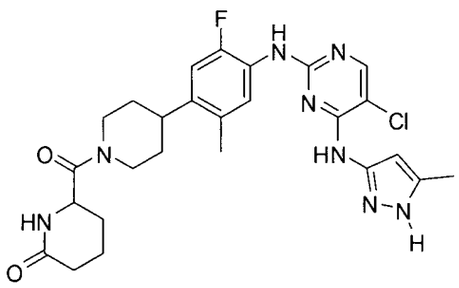
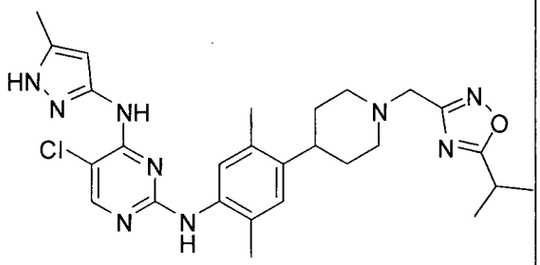
 azetidin-3-il-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-metanona	 1-óxido de 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-1-(tetrahidro-2H-piran-4-il)-piperidina
 (S)-azetidin-2-il-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-metanona	 5-cloro-N2-{4-[1-(1,1-dioxo-1λ6-tietan-3-il)-1-óxido-piperidin-4-il]-2-fluoro-5-metil-fenil}-N4-(5-etil-1H-pirazol-3-il)-pirimidin-2,4-diamina

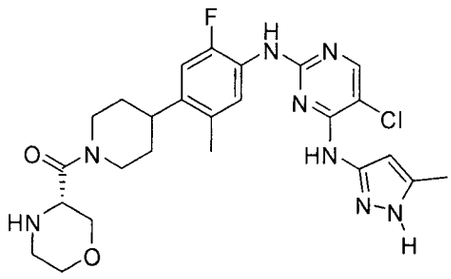
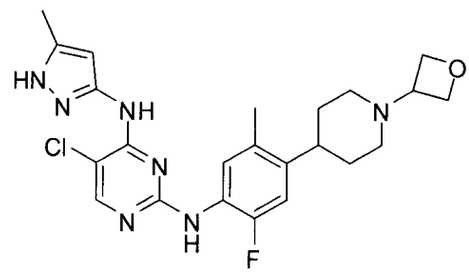
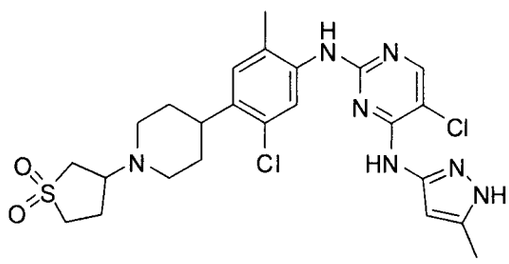
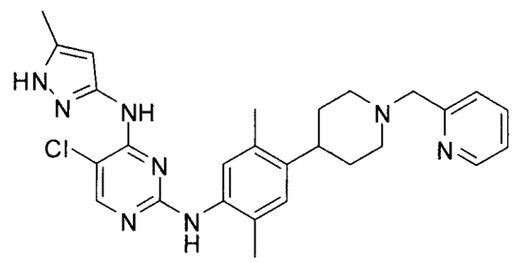
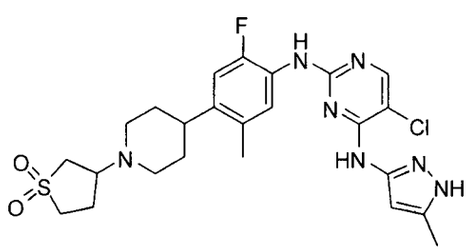
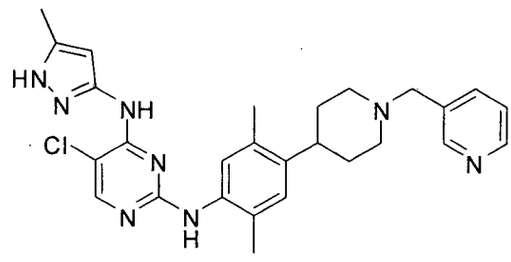
 (R)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-1-il)-(1-metil-pirrolidin-2-il)-metanona	 N2-(4-(1-(azetidin-3-il)-piperidin-4-il)-2-fluoro-5-metil-fenil)-5-cloro-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 (R)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-metil-pirrolidin-2-il)-metanona	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(piridin-3-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

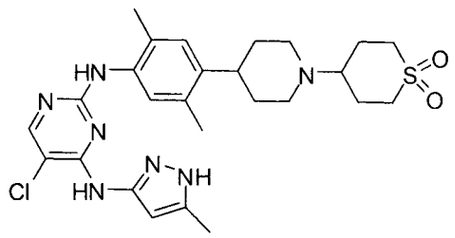
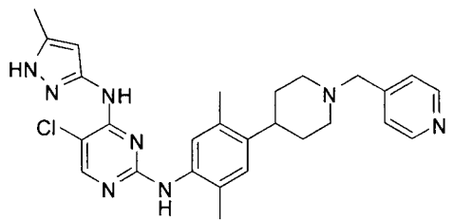
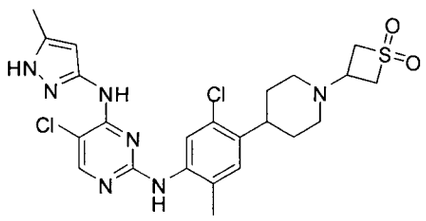
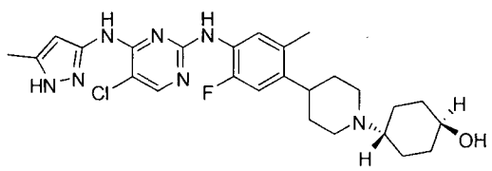
 (R)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1-isopropil-pirrolidin-2-il)-metanona	 4-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-ciclohexanol
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(4-metil-oxazol-5-il)-metanona	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(pirrolidin-3-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

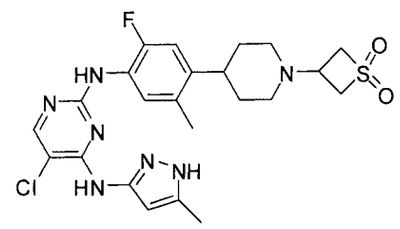
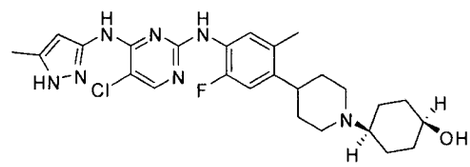
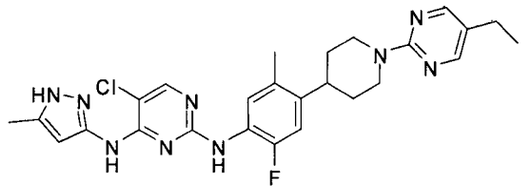
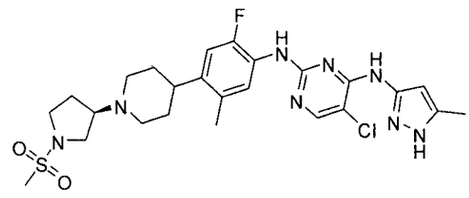
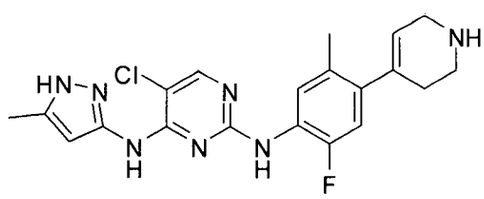
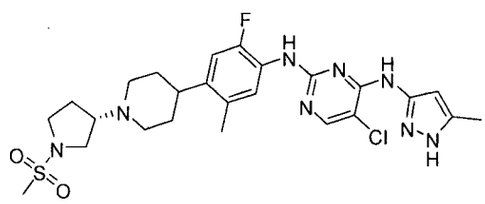
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(3,5-dimetil-isoxazol-4-il)-metanona	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(1-(metil-sulfonil)-azetidin-3-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 (S)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(2-metil-pirrolidin-2-il)-metanona	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(1-(metil-sulfonil)-pirrolidin-3-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

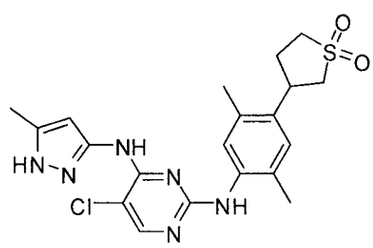
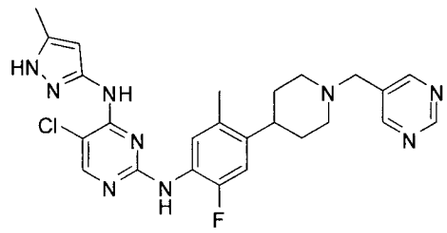
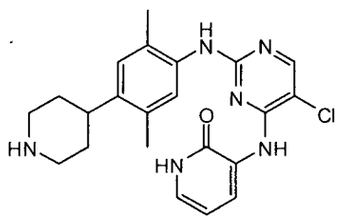
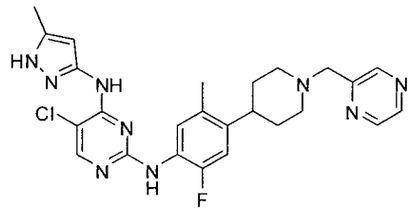
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-((2S,3R)-3-hidroxi-1-metil-pirrolidin-2-il)-metanona	 5-cloro-N2-(2,5-dimetil-4-(1-((3-metil-1,2,4-oxadiazol-5-il)-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(1H-tetrazol-1-il)-metanona	 5-cloro-N2-(4-(1-((3-etil-1,2,4-oxadiazol-5-il)-metil)-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

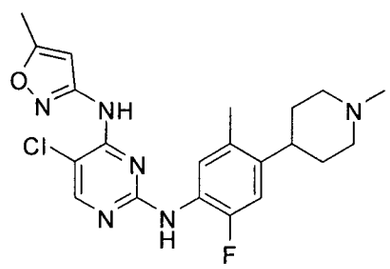
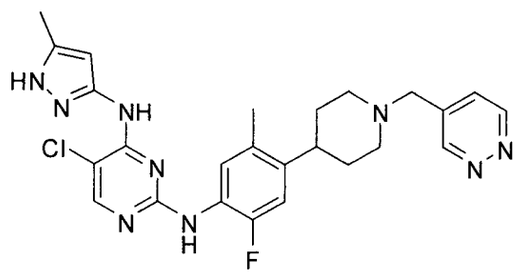
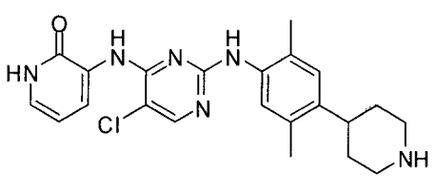
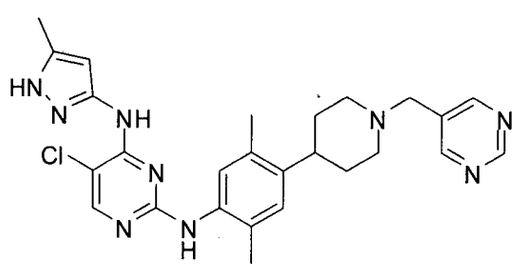
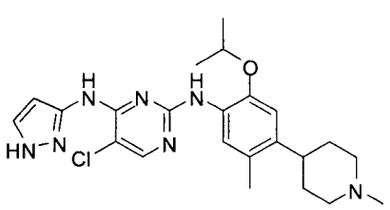
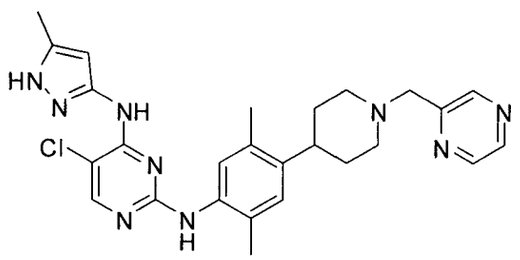
 (4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(2-metil-5-(trifluoro-metil)-oxazol-4-il)-metanona	 5-cloro-N2-(2,5-dimetil-4-(1-((5-metil-1,2,4-oxadiazol-3-il)-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 6-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-carbonil)-piperidin-2-ona	 5-cloro-N2-(4-(1-((5-isopropil-1,2,4-oxadiazol-3-il)-metil)-piperidin-4-il)-2,5-dimetil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

 (S)-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-(morfolin-3-il)-metanona	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(oxetan-3-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 5-cloro-N^2-(2-metil-5-cloro-4-(1-(tetrahidro-1,1-dioxido-3-tienil)-piperidin-4-il)-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina	 5-cloro-N2-(2,5-dimetil-4-(1-(piridin-2-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
	

5-cloro-N^2-(2-fluoro-5-metil-4-(1-(tetrahidro-1,1-dioxido-3-tienil)-piperidin-4-il)-fenil)-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina	5-cloro-N2-(2,5-dimetil-4-(1-(piridin-3-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 5-cloro-N2-(2,5-dimetil-4-(1-(tetrahidro-1,1-dioxido-2H-tiopiran-4-il))-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 5-cloro-N2-(2,5-dimetil-4-(1-(piridin-4-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 5-cloro-N2-(2-cloro-5-metil-4-(1-(1,1-dioxido-3-tietanil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 Trans-4-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-ciclohexanol

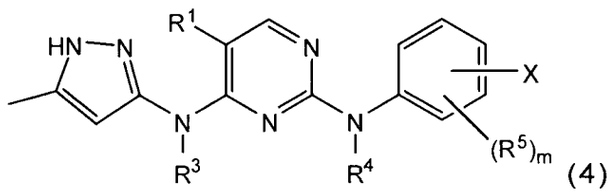
	
5-cloro-N2-(2-fluoro-5-metil-4-(1-(1,1-dioxido-3-tietanil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	Cis-4-(4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-5-fluoro-2-metil-fenil)-piperidin-1-il)-ciclohexanol
	
5-cloro-N2-(4-(1-(5-etil-pirimidin-2-il)-piperidin-4-il)-2-fluoro-5-metil-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	(R)-5-cloro-N2-(2-fluoro-5-metil-4-(1-(1-(metil-sulfonil)-pirrolidin-3-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
	
5-cloro-N2-(2-fluoro-5-metil-4-(1,2,3,6-tetrahidro-piridin-4-il)-	(S)-5-cloro-N2-(2-fluoro-5-metil-4-(1-(1-(metil-sulfonil)-pirrolidin-

fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	3-il)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 5-cloro-N^2-[4-(1,1-dioxo-tetrahidro-1□^{6}-tiofen-3-il)-2,5-dimetil-fenil]-N^4-(5-metil-1*H*-pirazol-3-il)-pirimidin-2,4-diamina	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(pirimidin-5-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 3-(5-cloro-2-(2,5-dimetil-4-(piperidin-4-il)-fenil-amino)-pirimidin-4-il-amino)-piridin-2(1H)-ona	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(pirazin-2-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

 5-cloro-N2-(2-fluoro-5-metil-4-(1-metil-piperidin-4-il)-fenil)-N4-(5-metil-isoxazol-3-il)-pirimidin-2,4-diamina	 5-cloro-N2-(2-fluoro-5-metil-4-(1-(piridazin-4-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 3-(5-cloro-2-(2,5-dimetil-4-(piperidin-4-il)-fenil-amino)-pirimidin-4-il-amino)-piridin-2(1H)-ona	 5-cloro-N2-(2,5-dimetil-4-(1-(pirimidin-5-il-metil)-piperidin-4-il)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina
 5-cloro-N2-(2-isopropoxi-5-metil-4-(1-metil-piperidin-4-il)-fenil)-N4-(1H-pirazol-3-il)-pirimidin-	 5-cloro-N2-(2,5-dimetil-4-(1-(pirazin-2-il-metil)-piperidin-4-il)-

2,4-diamina	fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

11. Un compuesto de la fórmula (4):



(4)

o una sal fisiológicamente aceptable del mismo;

en donde X es un anillo heterocíclico monocíclico de 5 a 6 miembros que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O, y S, y opcionalmente sustituido sobre un átomo de carbono del anillo sustituible con oxo y en cualquier átomo de nitrógeno del anillo sustituible por R^6;

R^1 es halógeno;

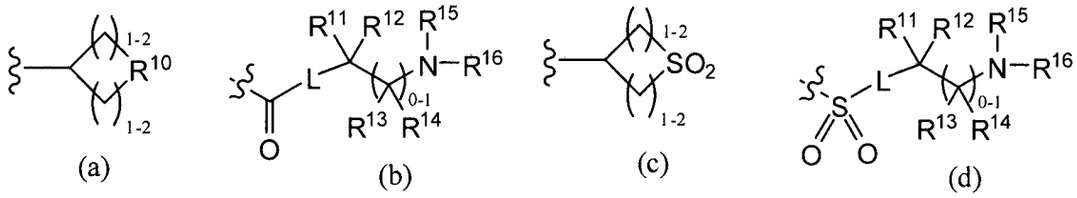
R^3 y R^4 son cada uno H;

R^5 es halógeno, hidroxilo, alquilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno, ciano o $C(O)O_{0-1}R^8$;

R^6 es H; alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con grupos halógeno y/o hidroxilo; $-(CR_2)_p-OR^7$, $-(CR_2)_p-CH(OH)C_tF_{2t+1}$ en

donde t es de 1 a 3, $(CR_2)_p$-CN; $(CR_2)_p$-NR(R^7), -$(CR_2)_p$–C(O)OR^7, $(CR_2)_p$NR$(CR_2)_p$OR^7, $(CR_2)_p$NR-L-C(O)R^8, C(O)-$(CR_2)_q$OR^8, -C(O)O-$(CR_2)_p$-NRR^7, –C(O) -$(CR_2)_p$-OR^7, L-Y, -L-C(O)R^7, -L–C(O)-NRR^7, -L–C(O)-NR-$(CR_2)_p$-NRR^7,-L-C(O)NR$(CR_2)_p$OR^7, -L–C(O)-$(CR_2)_q$-NR-C(O)-R^8, -L-C(O)NR$(CR_2)_p$SR^7, -L-C(O)NR$(CR_2)_p$S(O)$_{1-2}R^8$, -L-S(O)$_2R^8$, -L-S(O)$_2$-$(CR_2)_q$-NRR^7, -L-S(O)$_2$NR$(CR_2)_p$NR(R^7) o -L-S(O)$_2$NR$(CR_2)_p$OR^7;

de una manera alternativa, R^6 es un radical seleccionado a partir de la fórmula (a), (b), (c) o (d):



(a) (b) (c) (d)

R^{10} es O, S, NR^{17} en donde R^{17} es H, alquilo de 1 a 6 átomos de carbono, SO_2R^{8a} o CO_2R^{8a};

R^{11}, R^{12}, R^{13}, R^{14}, R^{15} y R^{16} se seleccionan independientemente a partir de H; alcoxilo de 1 a 6 átomos de carbono; alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con grupos halógeno, amino, o hidroxilo; o R^{11} y R^{12}, R^{12} y R^{15}, R^{15} y R^{16}, R^{13} y R^{14}, o R^{13} y R^{15}, junto con los átomos con los que están unidos, pueden formar un anillo de 3 a 7 miembros, saturado, insaturado, o parcialmente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O, y S, y opcionalmente sustituido con

oxo y de 1 a 3 grupos R^5;

L es $(CR_2)_{1-4}$ o un enlace;

Y es un anillo carbocíclico de 3 a 7 átomos de carbono, arilo de 6 a 10 átomos de carbono, o un heteroarilo de 5 a 10 miembros o anillo heterocíclico de 4 a 10 miembros, cada uno de los cuales está opcionalmente sustituido con 1 a 3 grupos R^5;

R^7, R^8 y R^{8a} son independientemente alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, o alquinilo de 2 a 6 átomos de carbono, cada uno de los cuales puede estar opcionalmente sustituido con halógeno, amino, hidroxilo o ciano; $(CR_2)_qY$ o alcoxilo de 1 a 6 átomos de carbono; o R^7 es H;

cada R es independientemente H o alquilo de 1 a 6 átomos de carbono;

R y R^7 junto con N en cada NRR^7 pueden formar un anillo de 5 a 6 miembros que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O, y S, y opcionalmente sustituido con oxo y de 1 a 3 grupos R^5;

m es de 2 a 4;

n es de 1 a 3;

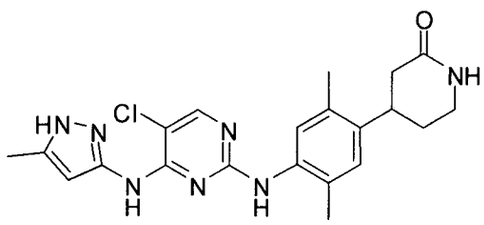
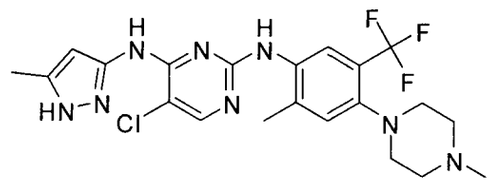
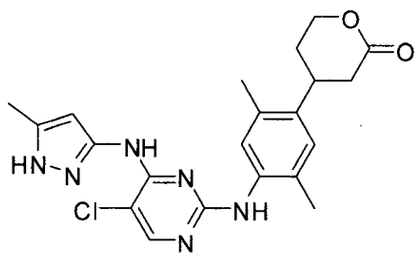
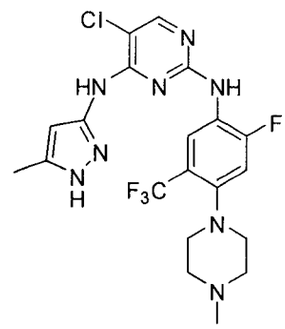
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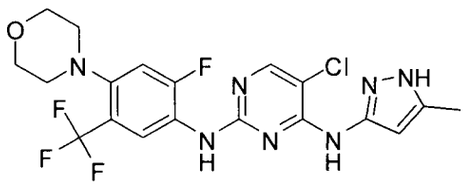
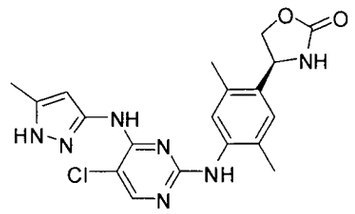
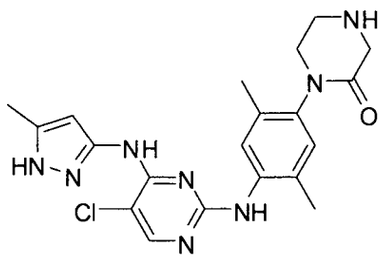
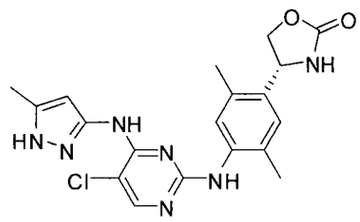
q es de 0 a 4.

12. El compuesto de la reivindicación 13, en donde X es morfolinilo, piperazinilo, piperazin-2-onilo, oxazolidin-2-onilo o piperidin-2-onilo, cada uno de los cuales está sustituido en cualquier átomo de nitrógeno del anillo sustituible por alquilo de 1 a 6 átomos

de carbono; o X es tetrahidro-2H-piran-2-onilo; y R^1 es cloro.

13. El compuesto de la reivindicación 12, en donde el compuesto mencionado se selecciona a partir del grupo que consiste en:

 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperidin-2-ona	 5-cloro-N4-(5-metil-1H-pirazol-3-il)-N2-(2-metil-4-(4-metil-piperazin-1-il)-5-(trifluoro-metil)-fenil)-pirimidin-2,4-diamina
 4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-tetrahidro-2H-piran-2-ona	 5-cloro-N2-(2-fluoro-4-(4-metil-piperazin-1-il)-5-(trifluoro-metil)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina

 5-cloro-N2-(2-fluoro-4-morfolino-5-(trifluoro-metil)-fenil)-N4-(5-metil-1H-pirazol-3-il)-pirimidin-2,4-diamina	 (S)-4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-oxazolidin-2-ona
 1-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-piperazin-2-ona	 (R)-4-(4-(5-cloro-4-(5-metil-1H-pirazol-3-il-amino)-pirimidin-2-il-amino)-2,5-dimetil-fenil)-oxazolidin-2-ona

14. Una composición farmacéutica, la cual comprende una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1 a 13, y un vehículo fisiológicamente aceptable.

15. Un método para inhibir IGF-1R en una célula, el cual comprende poner en contacto la célula con una cantidad efectiva de

un compuesto de cualquiera de las reivindicaciones 1 a 13, o con una composición farmacéutica del mismo.

16. Un método para el tratamiento de una condición mediada por IGF-1R en un mamífero que sufra de la misma, el cual comprende administrar al mamífero una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1 a 13, o una composición farmacéutica del mismo, y opcionalmente en combinación con un segundo agente terapéutico; en donde esta condición es una enfermedad autoinmune, una enfermedad por trasplante, una enfermedad infecciosa, o un trastorno proliferativo celular.

17. El método de la reivindicación 16, en donde esta condición es un trastorno proliferativo celular.

18. El método de la reivindicación 17, en donde el trastorno proliferativo celular mencionado es mieloma múltiple, neuroblastoma, sarcoma sinovial, hepatocelular, de Ewing, o un tumor sólido seleccionado a partir de un osteosarcoma, melanoma, y tumor de mama, renal, de próstata, colo-rectal, de tiroides, de ovario, pancreático, de pulmón, uterino, o un tumor gastrointestinal.

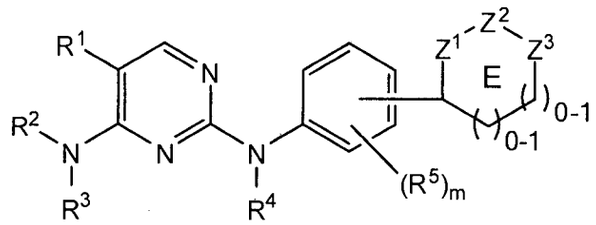
19. El método de la reivindicación 16, en donde el segundo agente terapéutico es un agente quimioterapéutico.

20. El uso de un compuesto de cualquiera de las reivindicaciones 1 a 13, o de una composición farmacéutica del mismo, para la fabricación de un medicamento para el tratamiento de una condición mediada por IGF-1R o por cinasa de linfoma

anaplásico, y opcionalmente en combinación con un segundo agente terapéutico, en donde esta condición es una enfermedad autoinmune, una enfermedad por trasplante, una enfermedad infecciosa, o un trastorno proliferativo celular.

RESUMEN

La invención proporciona novedosos derivados de pirimidina de la fórmula 1:



(1)

y composiciones farmacéuticas de los mismos, y métodos para utilizar estos compuestos. Por ejemplo, los derivados de pirimidina de la invención se pueden utilizar para tratar, aminorar o prevenir una condición que responda a la inhibición del factor de crecimiento tipo insulina (IGF-1R) o de la cinasa de linfoma anaplásico (ALK).

* * * * *

PATENT COOPERATION TREATY

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, California 92121
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
03 December 2010 (03.12.2010)

Applicant's or agent's file reference
P1340PC20

IMPORTANT NOTIFICATION

International application No.
PCT/US2009/048428

International filing date *(day/month/year)*
24 June 2009 (24.06.2009)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address
IRM LLC
131 Front Street,
P.O. Box 2899
Hamilton, HM LX
Bermuda

State of Nationality: US
State of Residence:
Telephone No.: (858) 812-1539
Facsimile No.: (858) 812-1909
E-mail address: iplegal@gnf.org

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
IRM LLC
131 Front Street
P.O. Box HM 2899
Hamilton, HM LX
Bermuda

State of Nationality: US
State of Residence: US
Telephone No.: (858) 812-1539
Facsimile No.: (858) 812-1909
E-mail address: iplegal@gnf.org
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 87 20

Authorized officer
Mazoillier Auguste
e-mail pt03.pct@wipo.int
Telephone No. +41 22 338 74 03

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Name and Address
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Name and Address
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Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☒ the nationality ☐ the residence

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San Diego, California 92128
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1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

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LU, Wenshuo
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State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
LU, Wenshuo
3644 Berryfield Court
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United States of America

State of Nationality: CA
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
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Authorized officer
Mazoillier Auguste
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Telephone No. +41 22 338 74 03

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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-008053- -00000-0000

Fecha: 2011-01-25 17:07:32 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 334

PATENTE DE INVENCIÓN ☐ MODEI

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☑ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☑ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☑ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

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Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
IRM LLC

REFERENCIA	Radicación No.	11 008053
	Solicitud internacional	PCT/US2009/048428
	Fecha inicio fase nacional	25/01/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	106086

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 consideraró 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.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (c)

08 ABR 2011

El anterior requerimiento fue notificado por fijación en lista de fecha_____.
adpa11

337

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
IRM LLC

REFERENCIA	Radicación No.	11 008053
	Solicitud internacional	PCT/US2009/048428
	Fecha inicio fase nacional	25/01/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	06087

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (c)

08 ABR. 2011

El anterior requerimiento fue notificado por fijación en lista de fecha_____.
adpa11